A Systems Approach for Understanding Cell Signaling

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Battelle

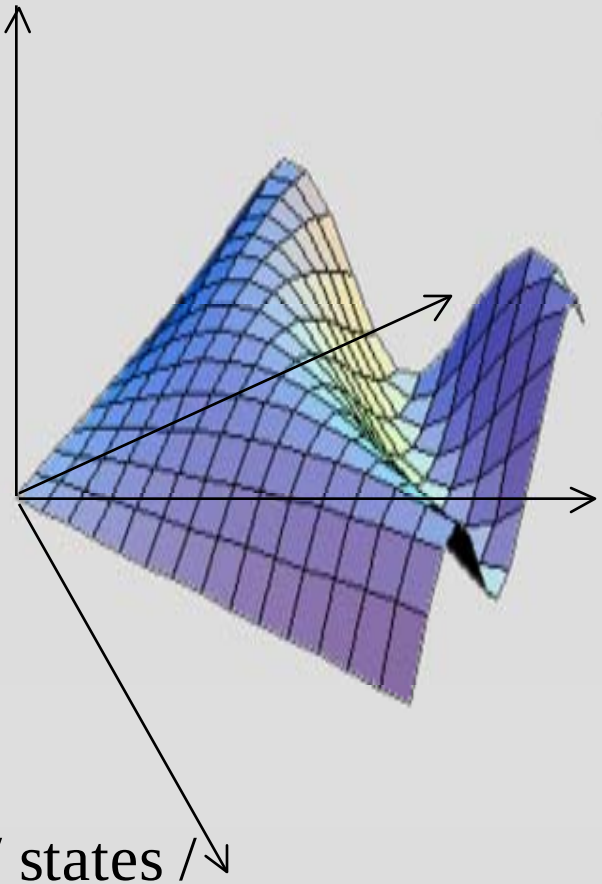
Bio Molecular Systems

What is a "Systems Approach" in the Context of Biological Organisms?

- Looking at cells as integrated systems and not as mere collections of parts
- Seeks to understand how changes in any given component will affect the behavior of the entire system
- Requires integration of information from molecular biology, biochemistry, physics and genetics to understand relationship between different sets of scientific data.
- Goal is a "Higher order" understanding of life processes.

Systems Perspective

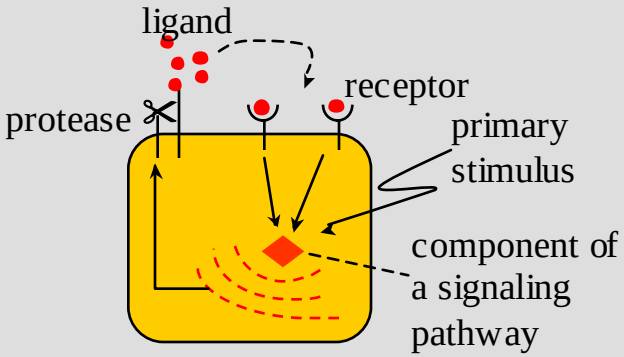
Cell function:
death,
proliferation,
differentiation,
migration, ...



Molecular parameters:
protein levels / states / locations / interactions / activities

Ultimate aim:
Understanding and prediction of effects of component properties

Currently, individual Investigators work on a small part of a larger problem

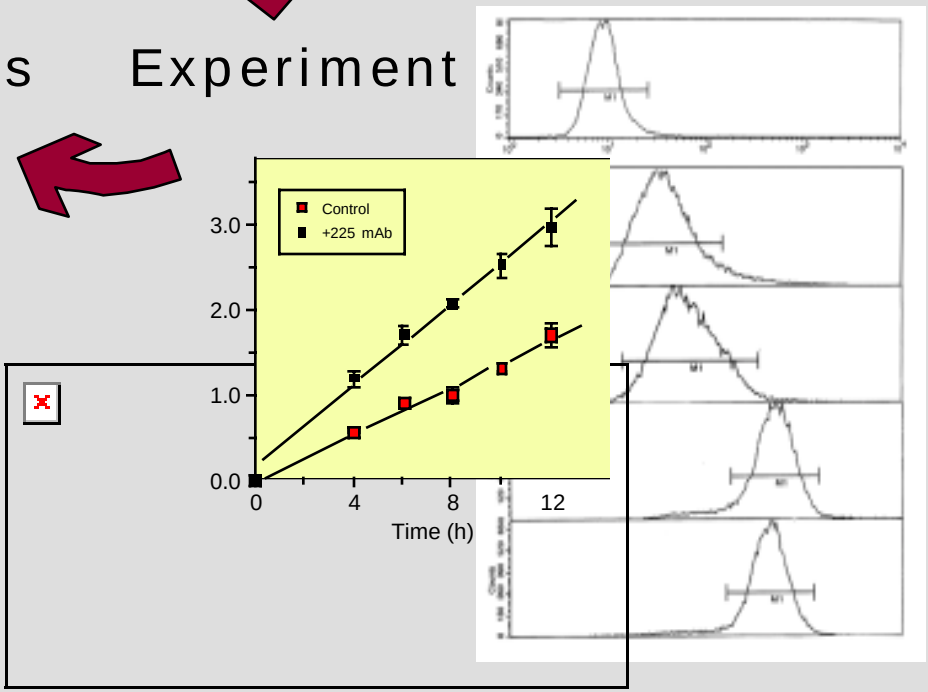


Theory

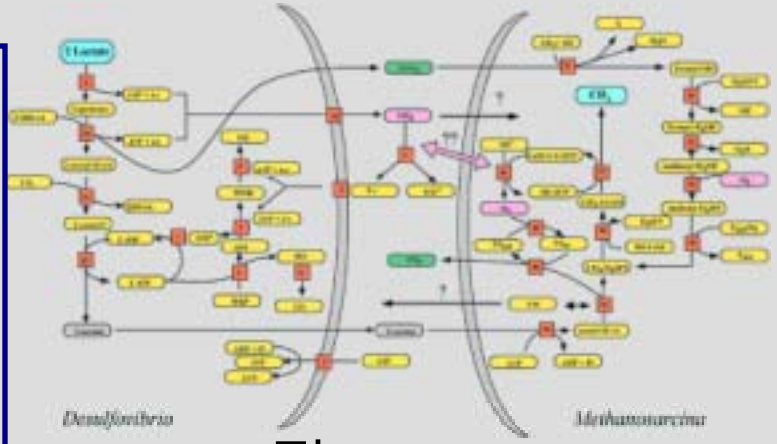
Analysis

Experiment

Cell line	EGFR	HER2
Parental (184A1 HMEC)	~2x10^5	~2x10^4
HER2 clone 29L	~2x10^5	~1x10^5
HER2 clone 12	~2x10^5	~2x10^5
HER2 clone 24H	~2x10^5	~8x10^5
HER2 clone 1	~2x10^5	~8x10^5



To understand organisms from a "systems perspective," it is necessary to integrate a large quantity of information



Metabolic and regulatory models

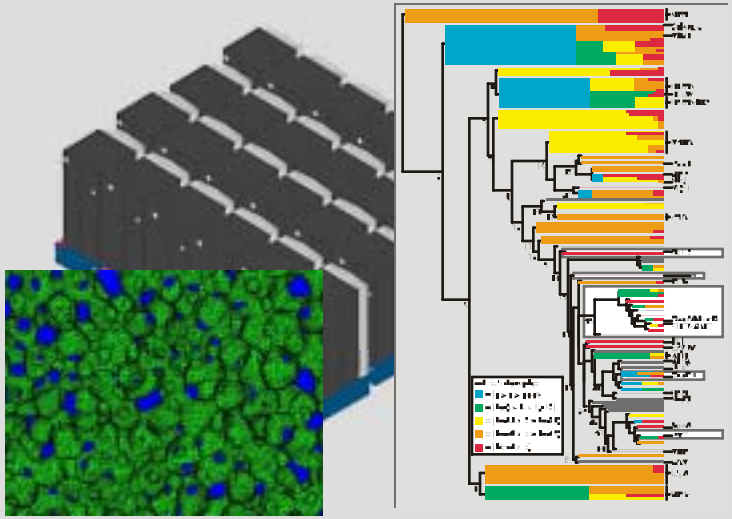
Theory

Advanced Computation and Information Management

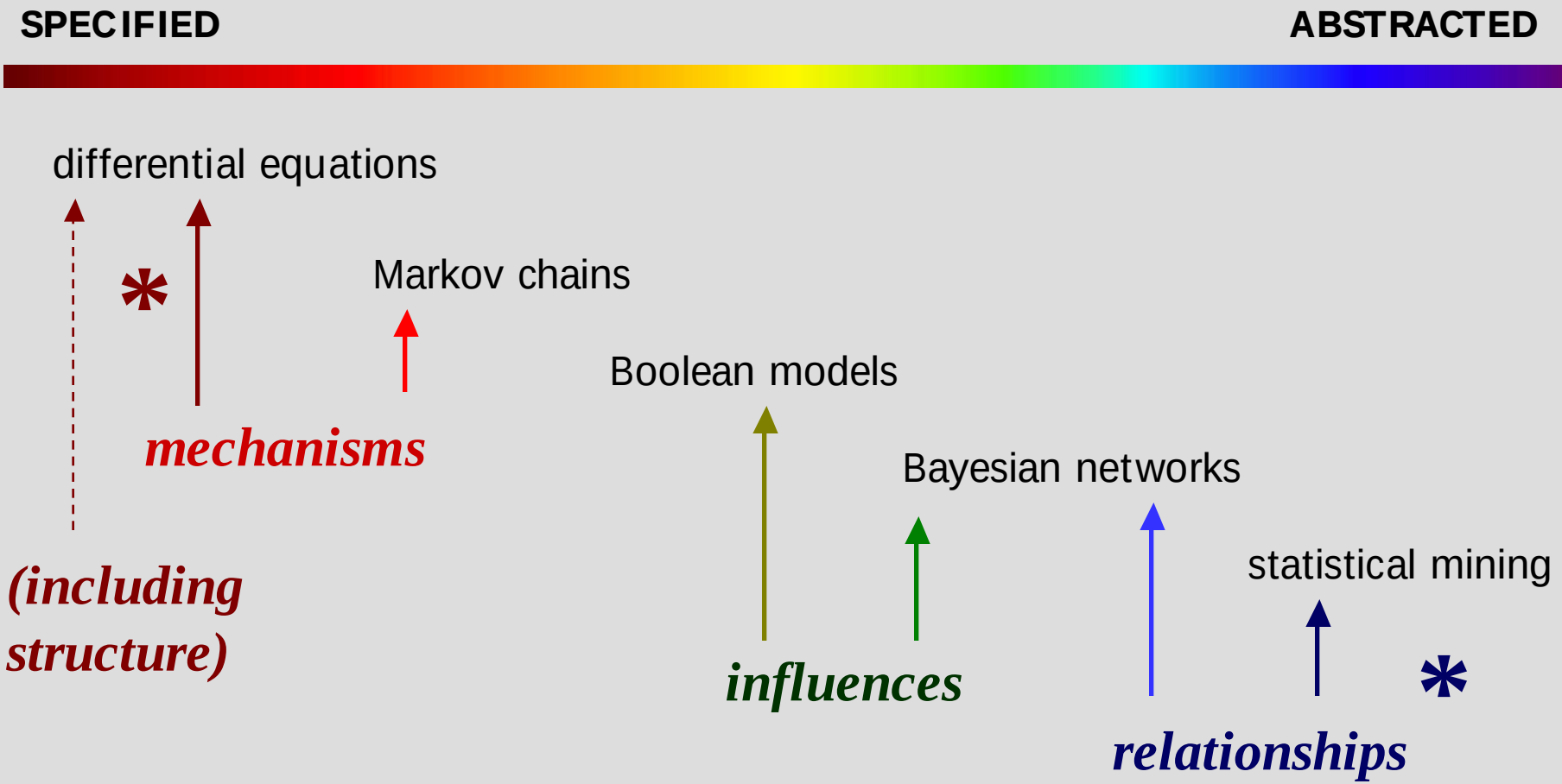
Analysis

Experiment

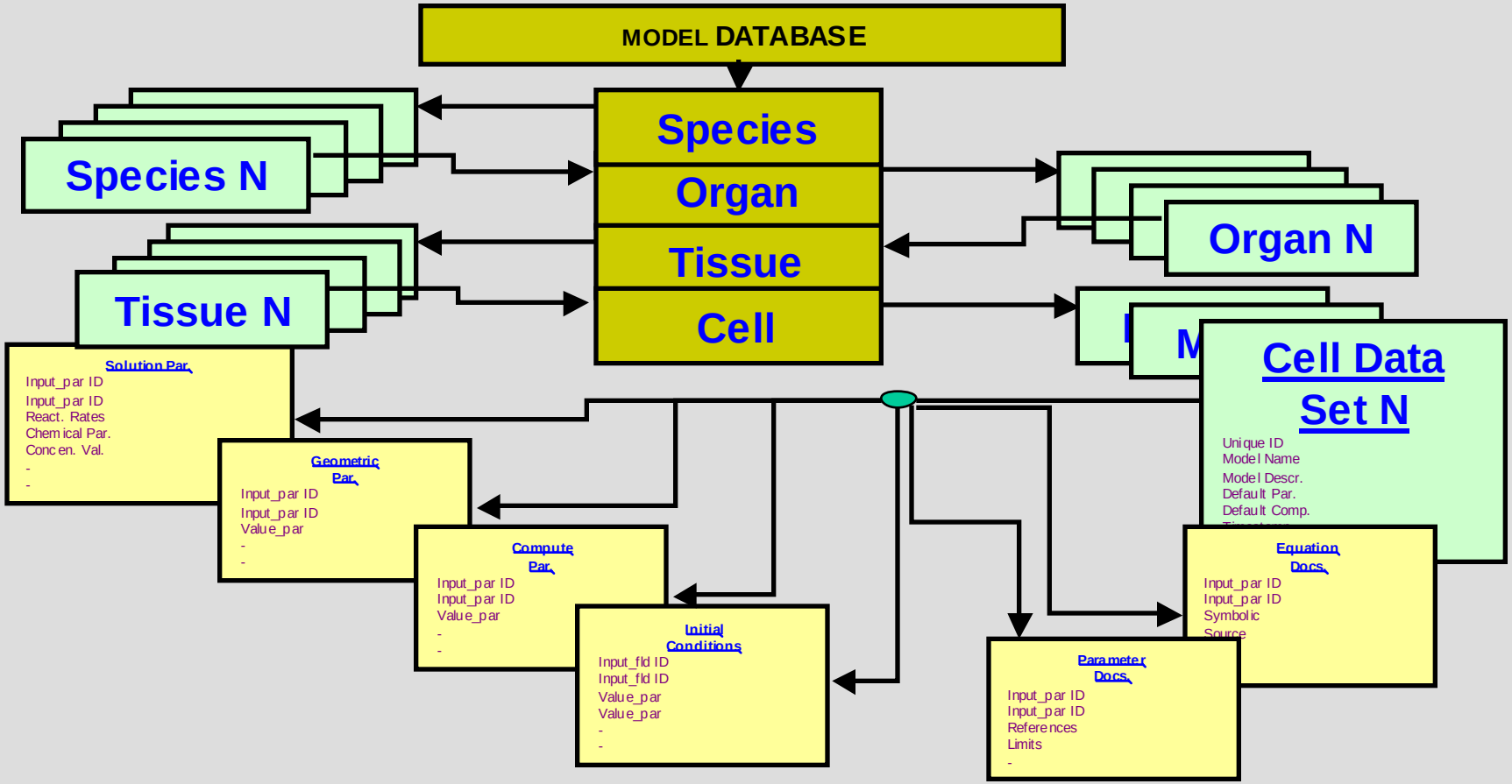
Advanced High-Throughput Technologies



Computational Modeling Approaches -- Diverse Spectrum



Computer Models Allow Reconstruction of Processes Across Different Scales



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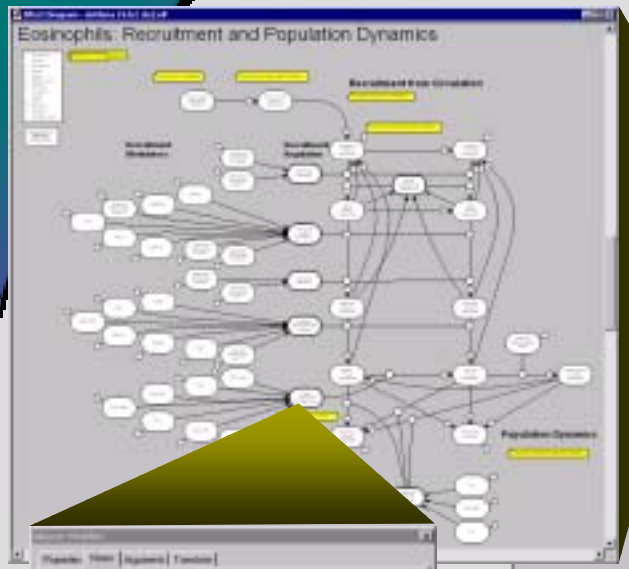
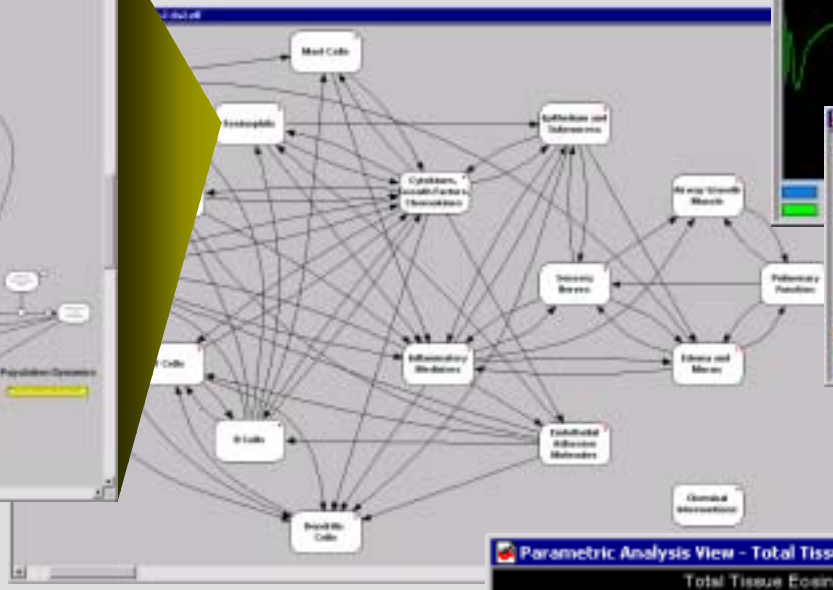
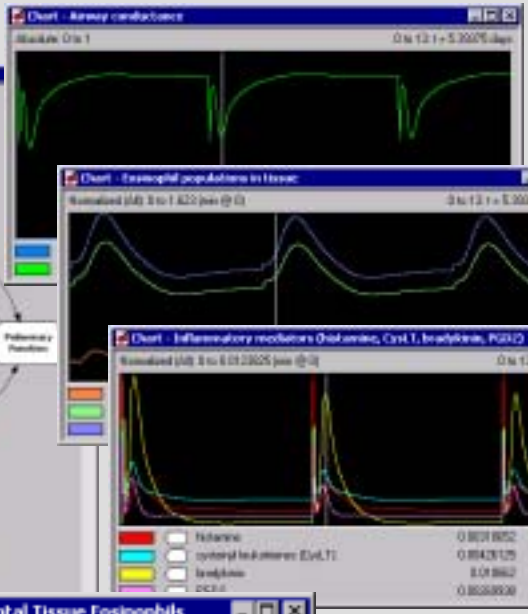
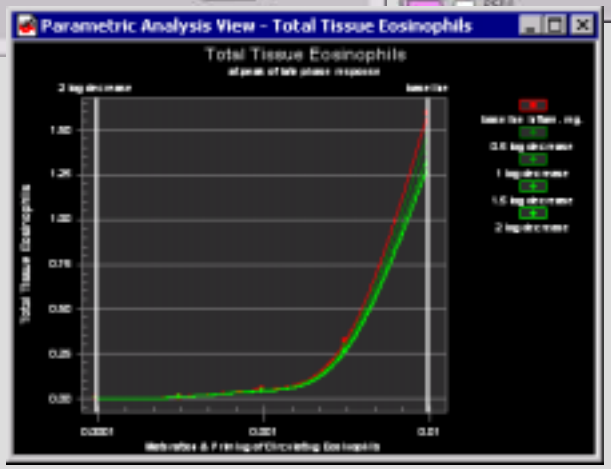


Disease Map







Simulation

Reference Database

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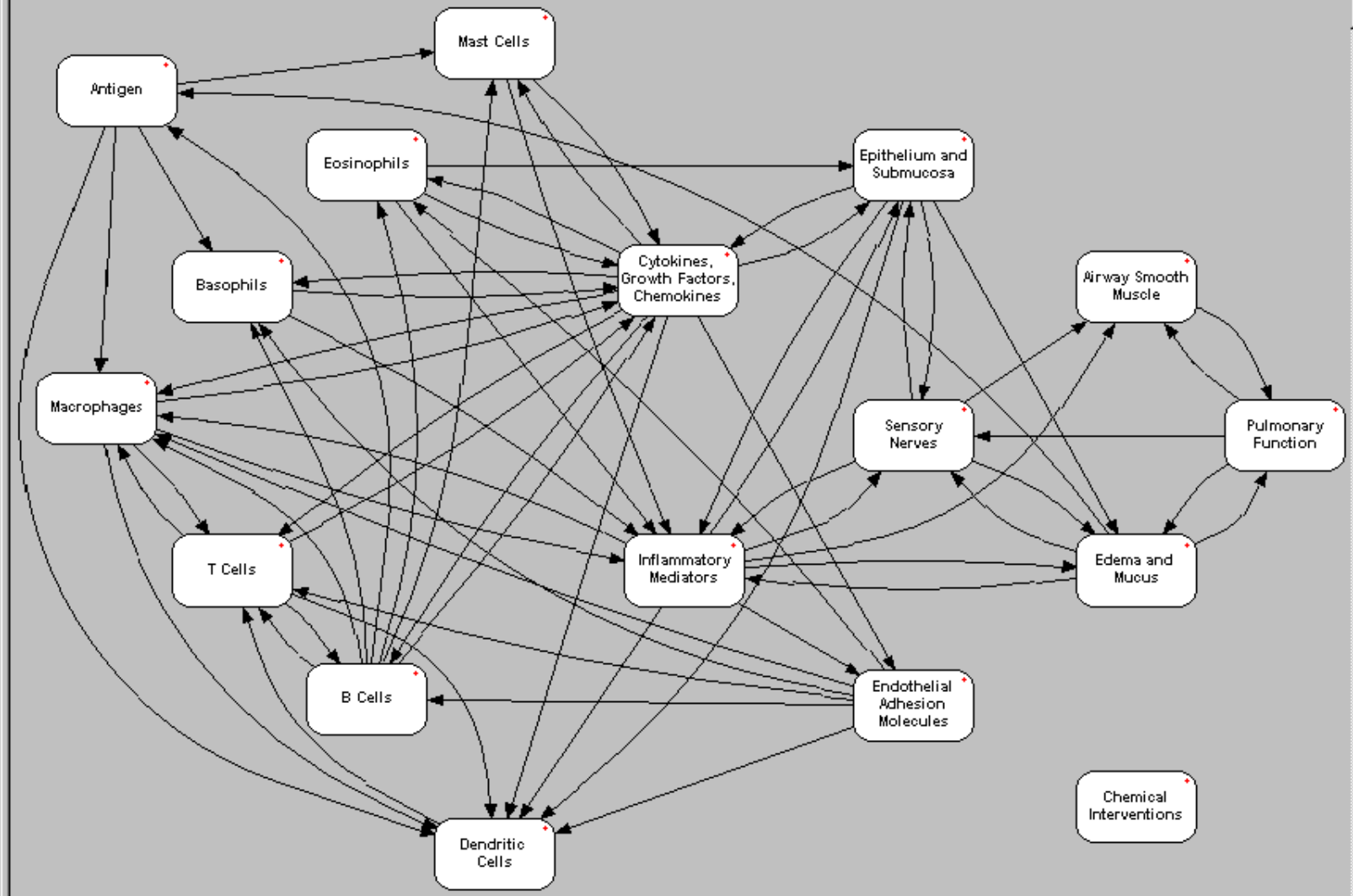
- Active Sets



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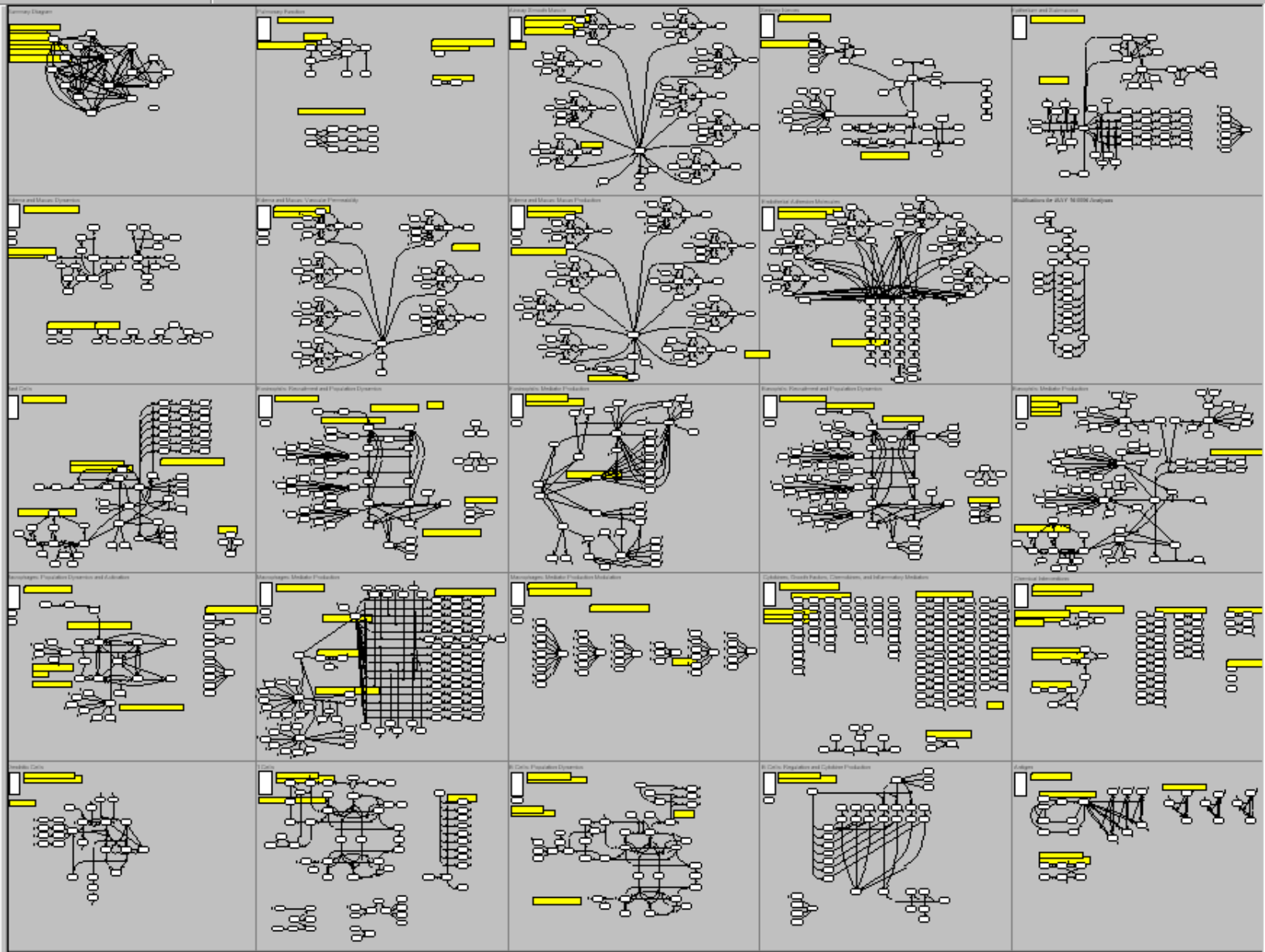

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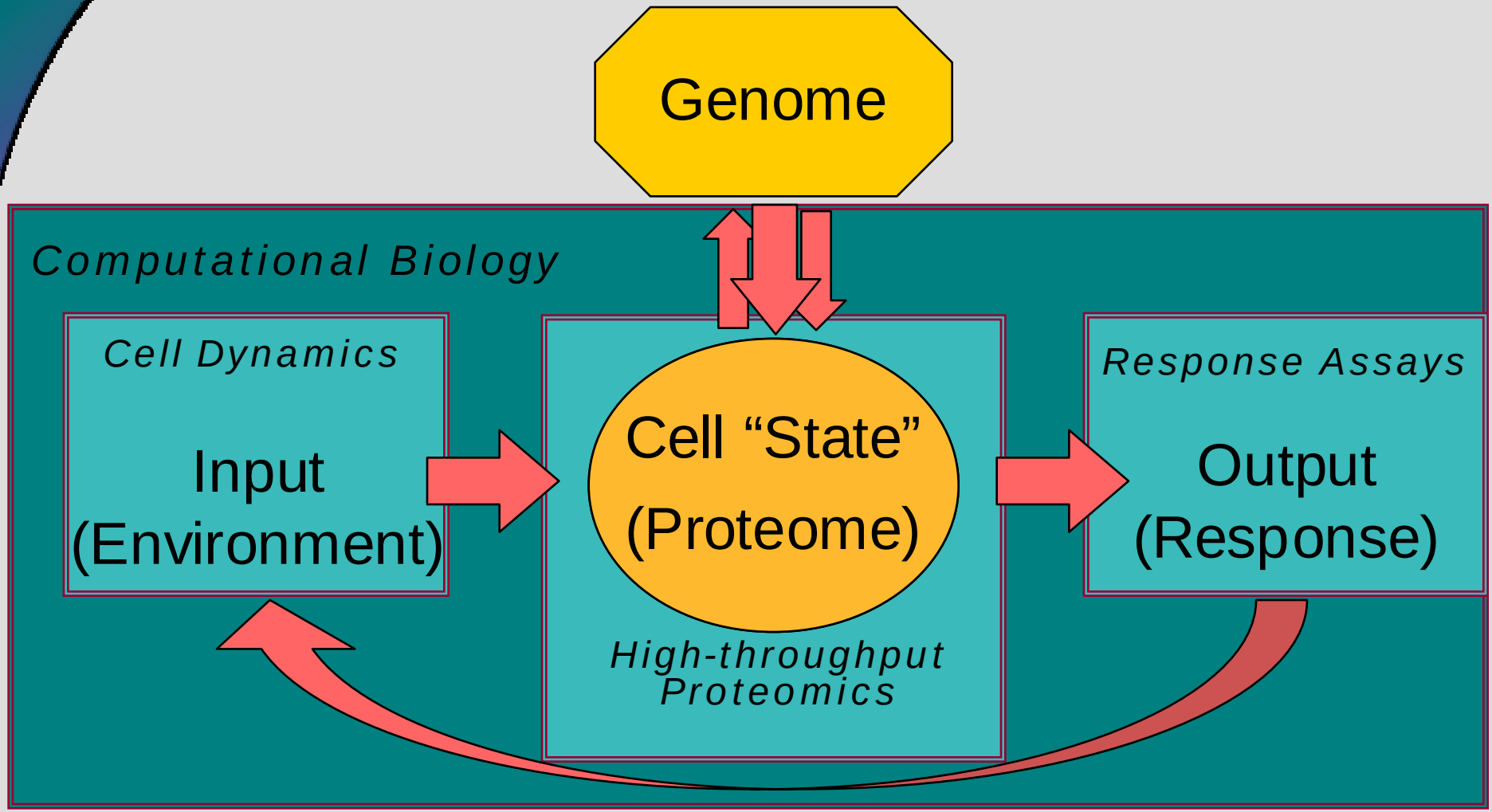
Variable Nature of Cells Confounds Structured Models of Systems

- The lowest functional level of physiological models is the cell
- It is relatively easy to specify a static input-output relationship of cells
- How do we account for variable input-output state?
- Dealing with recursive nature of cells is essential for creating realistic physiological models

Biological Organisms are Dynamic and Recursive

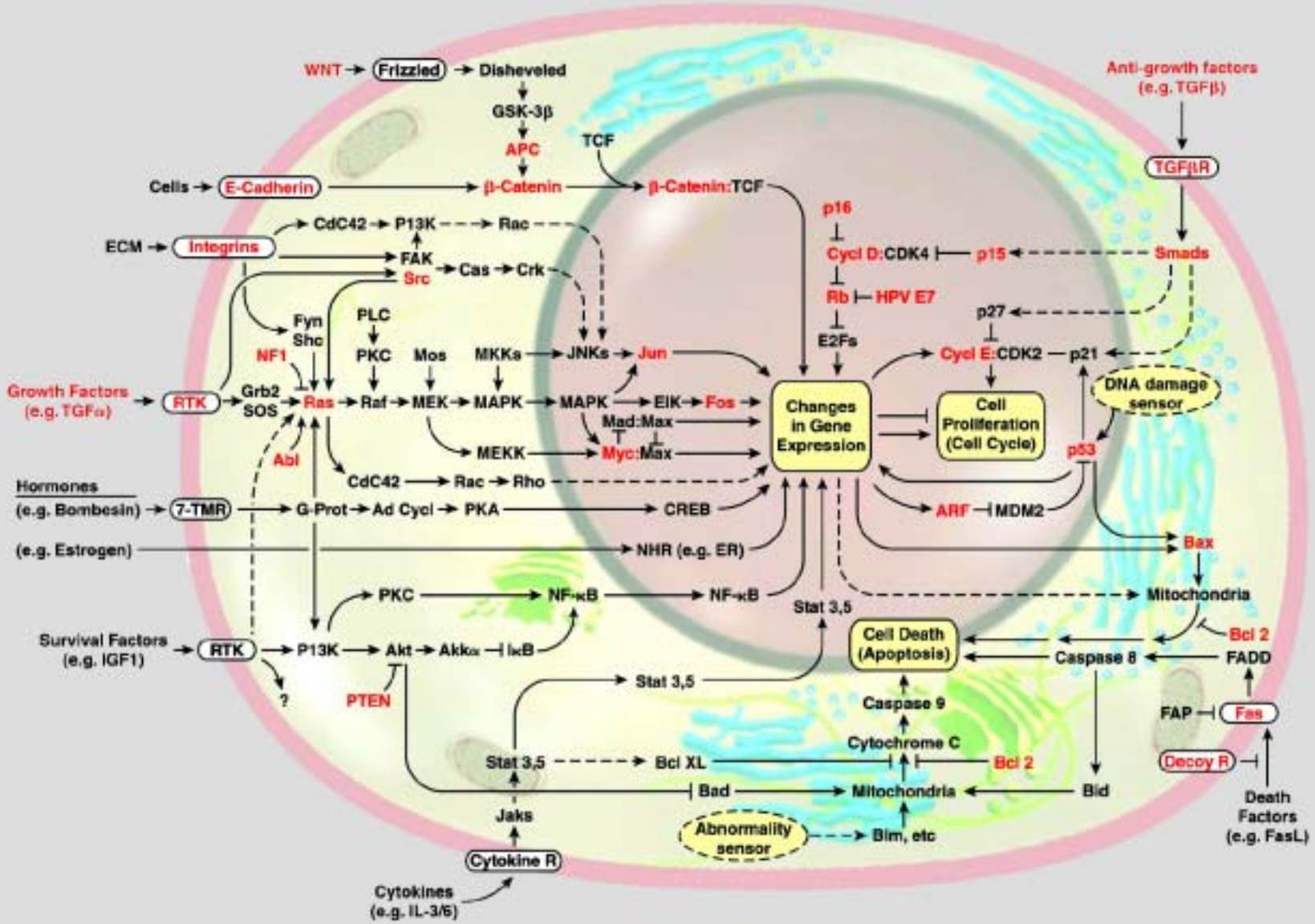


What, Where, Quantity, Quality?

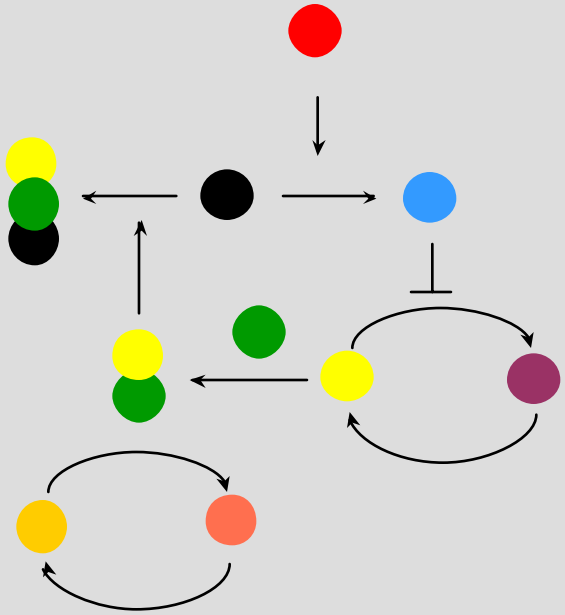
To successfully model a complex biological system, one must minimally know the following information:

- What parts are being made? (identity)
- Where are the proteins located in cell? (location)
- What are their levels? (quantity)
- How do they interact with their partners? (activity)
  - As a function of covalent modification
  - Contribution of steric restrictions
  - Forward and reverse rate constants

Cells are Regulated by a Network of Proteins



What Is Necessary to Understand a Network?



Nodes
(Components)

Connectivity
(Interactions)

Experimental Biology

Spatial Organization
(Transport)

Dynamic Range
(Kinetics)

Modeling & Analysis

Proteomics is Essential for Understanding Cellular Behavior

One cannot adequately model or predict cellular responses UNLESS the proteome of a given cell is first specified!

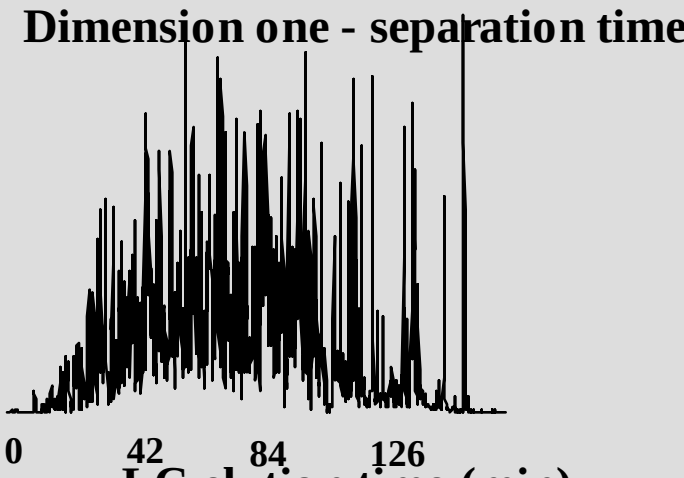
Proteomics Capabilities

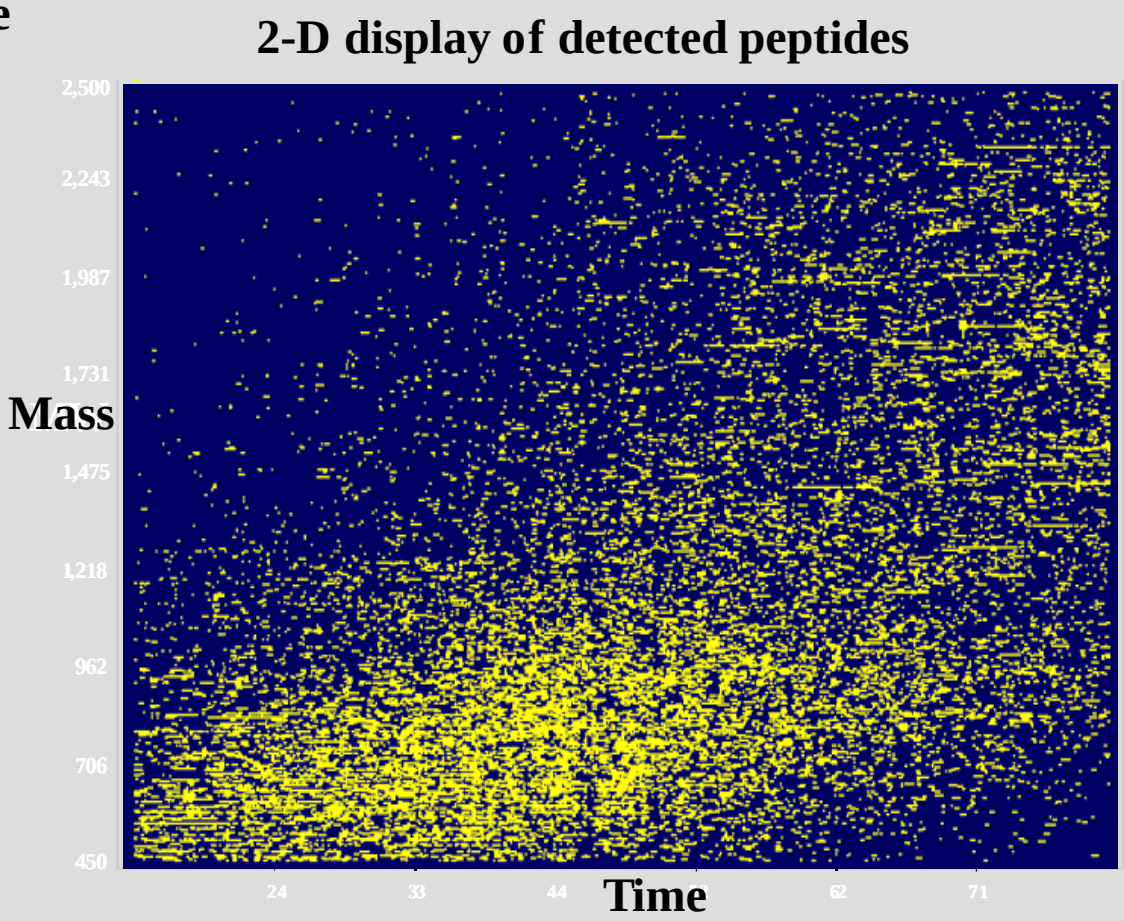
Unique method for rapid generation of synthetic antibodies using high-speed flow cytometers.

FTICR instruments provide unprecedented detail on the proteins expressed by cells under specific environmental conditions.

Global simultaneous quantitative proteome measurements

Proteins identified and quantified using accurate mass and time (AMT) tags





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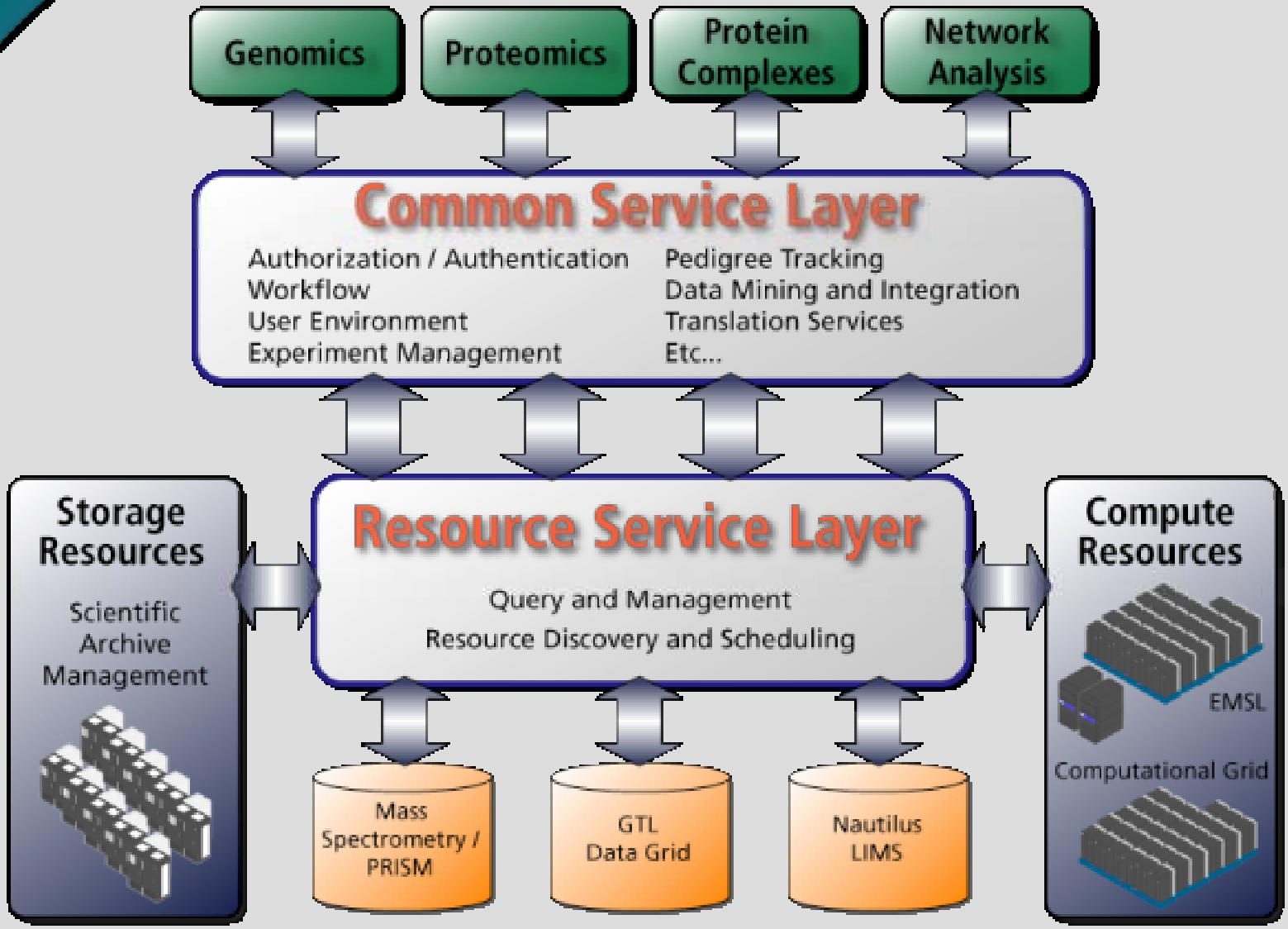
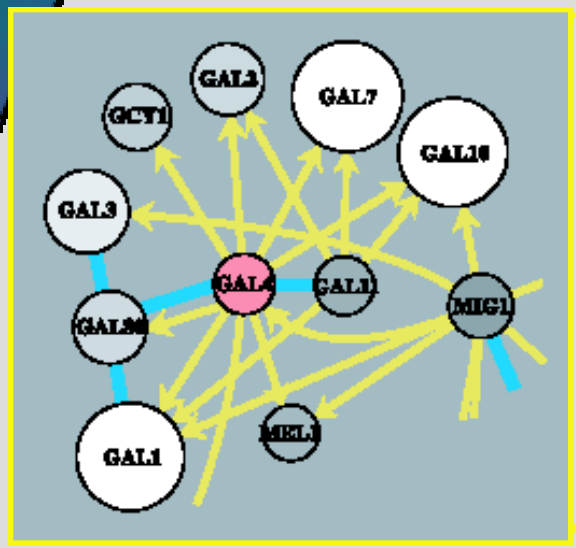
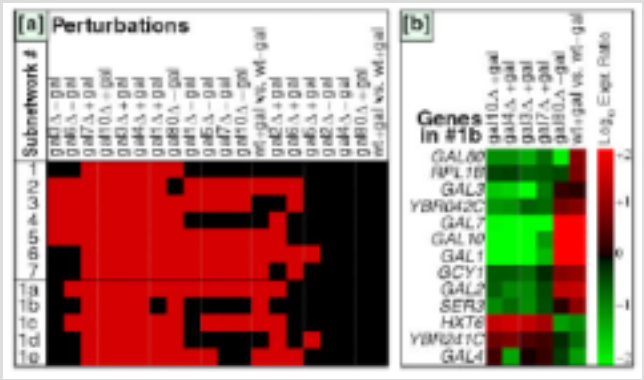
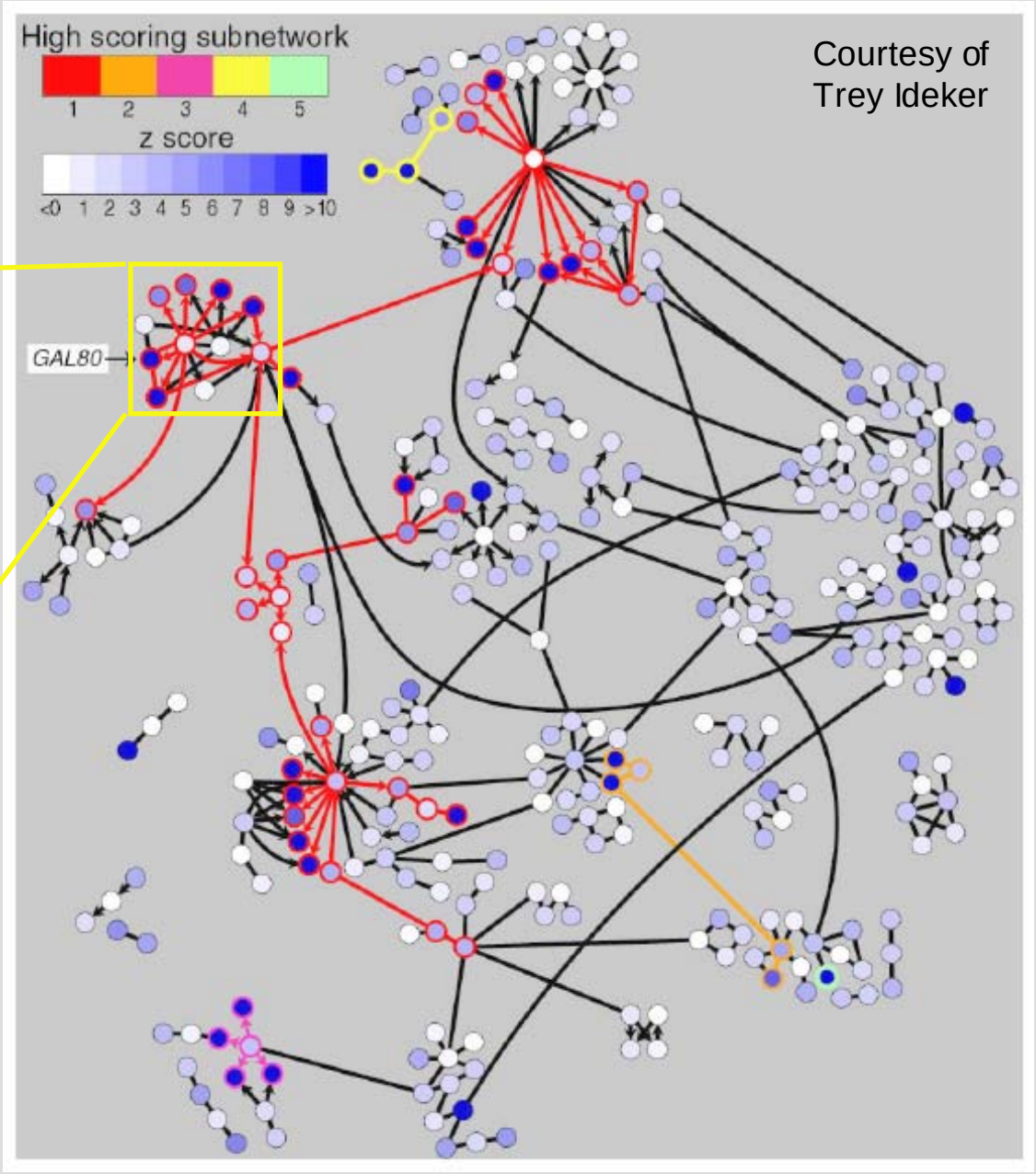
Problem Solving Environment

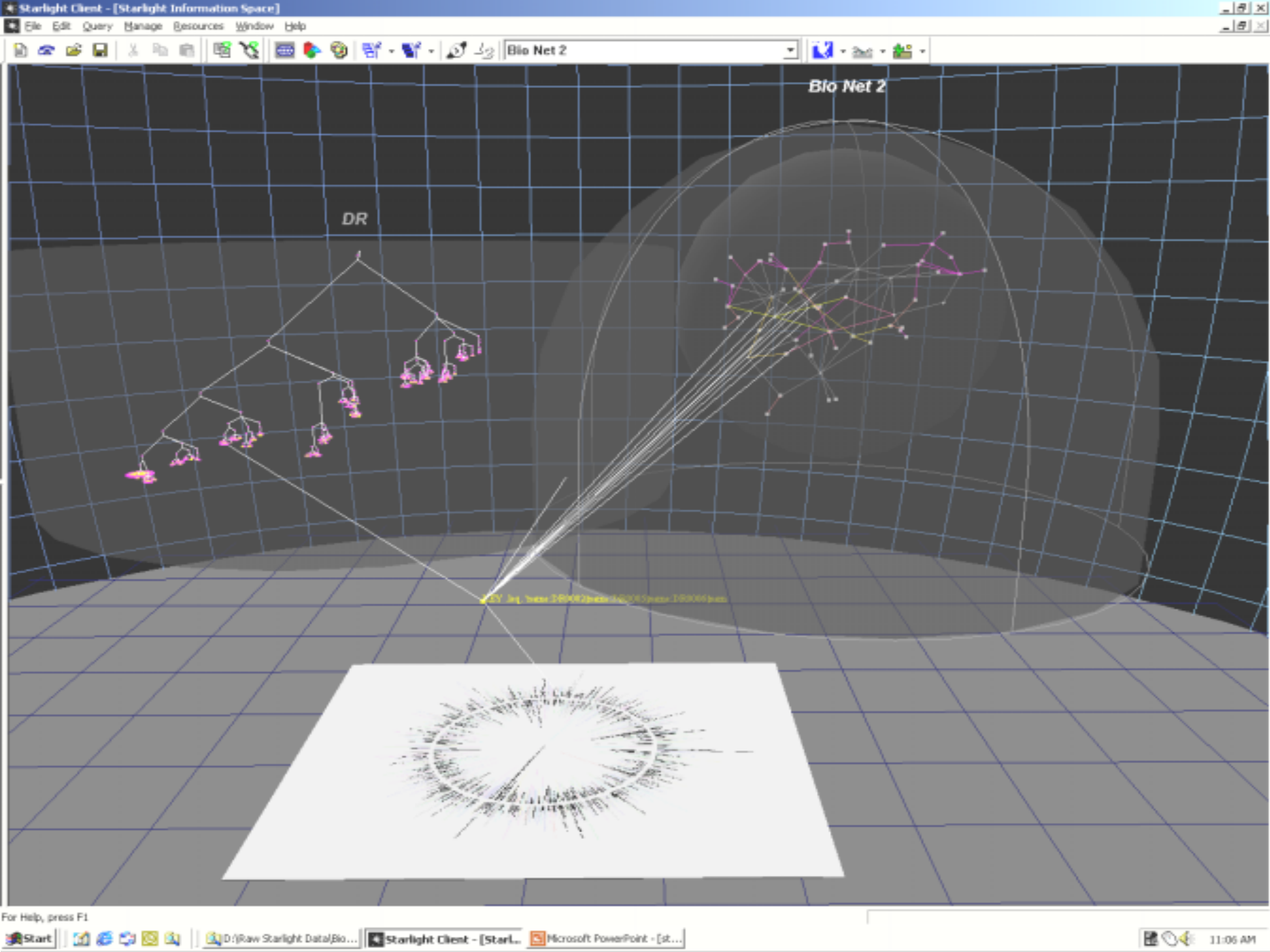


Evaluating interaction networks with gene expression data





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nature

27 January 2000 Volume 403 Issue no 6768

Can biological phenomena be understood by humans?

Despite the increasingly successful collaboration between physics and biology, there are contexts in which their styles and philosophies can diverge. Nowhere more so than in 'understanding'.

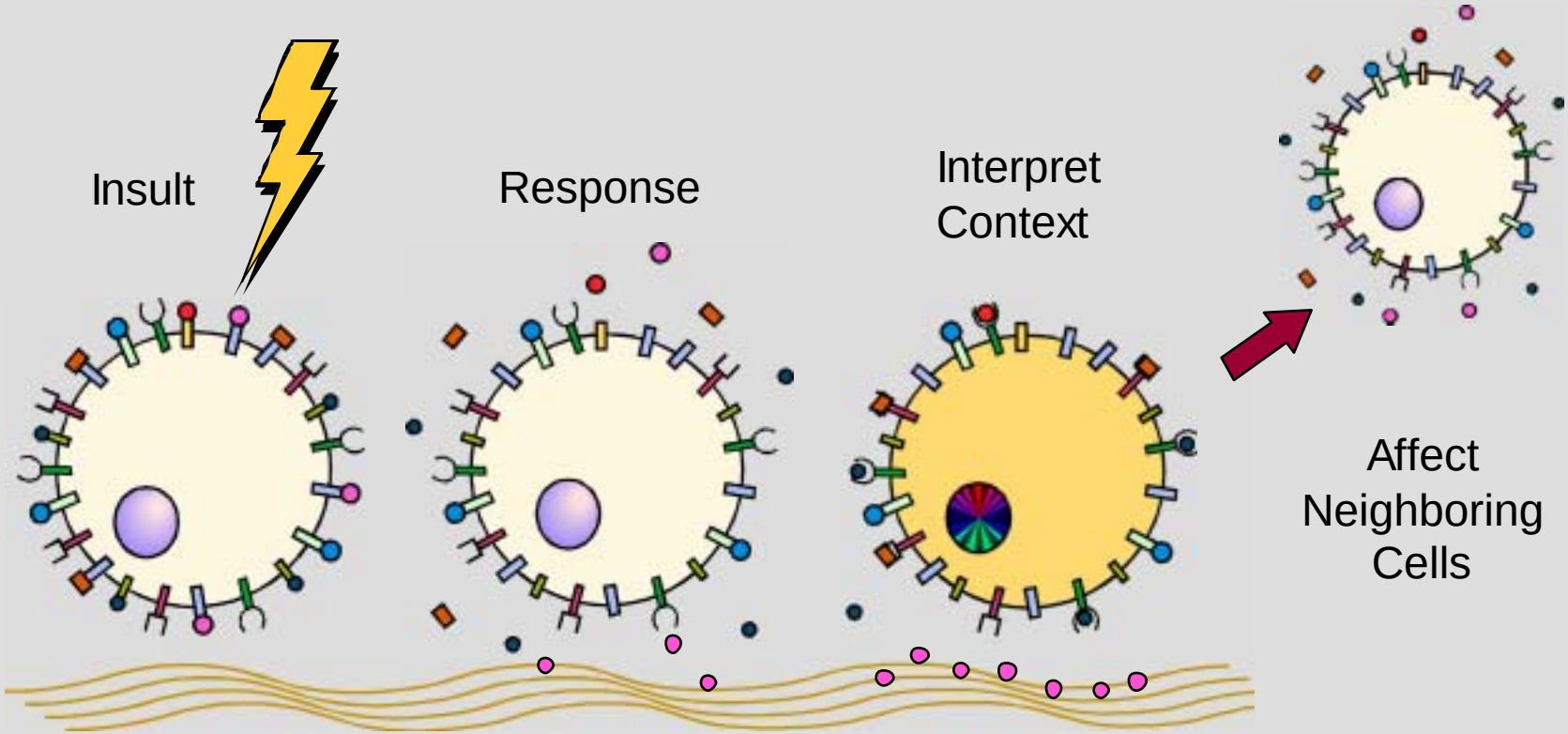
"It is nice to know that the computer understands the problem. But I would like to understand it, too." So said the theoretical physicist Eugene Wigner when shown the results of a large quantum mechanics calculation. Now, if a theoretical physicist of a younger generation is to be believed, today's biologists are in danger of delegating to their computers the job of understanding biology. Physics Nobel laureate Robert Laughlin — who was able to understand the fractional quantum Hall effect without the aid of computers — was invited to a conference in San Diego earlier this month on quantitative challenges in the post-genome-sequence era. His job was to stir things up, and he duly did so. His remarks sparked a spirited defence of the post-genome-sequence biological agenda, but also prompted some

Laughlin worries that in the post-genome era, biologists will be too busy accumulating facts and modelling them to seek simplification and underlying principles. The fact-gathering tendency is apparent not just in structural genomics, but also in functional genomics (where the aim is to identify the role of each gene in the genome) and proteomics (with a similar aim for each protein in the cell or organism). Evidently, there are enough facts to keep biologists busy gathering them for decades, so when will they have time to think?

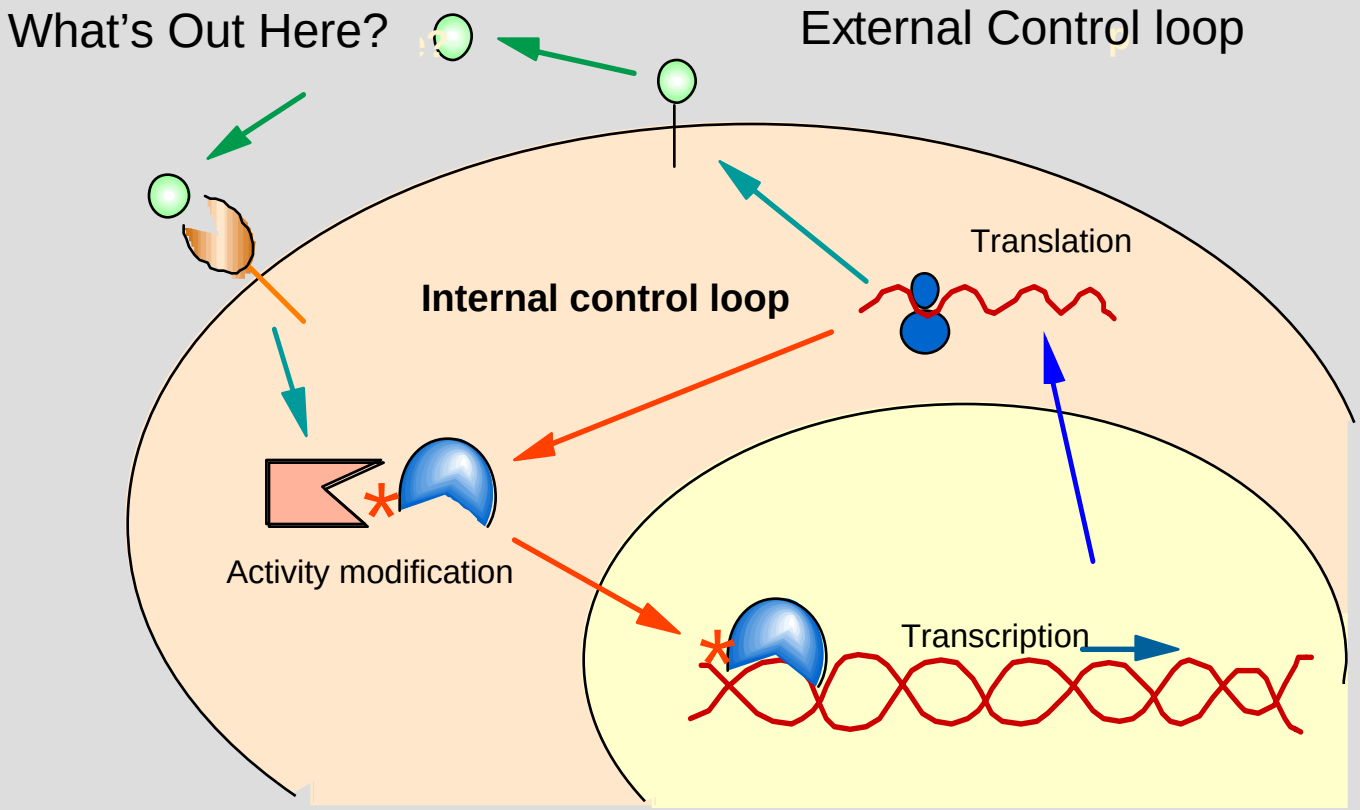
In defence of modelling

One answer, conveyed forcefully at the conference by Klaus Schulten (for protein-structure studies) and David Botstein (for

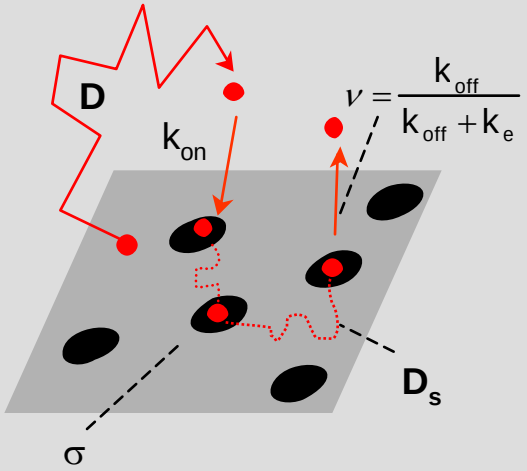
Model of How Cells Respond to a General Stressor

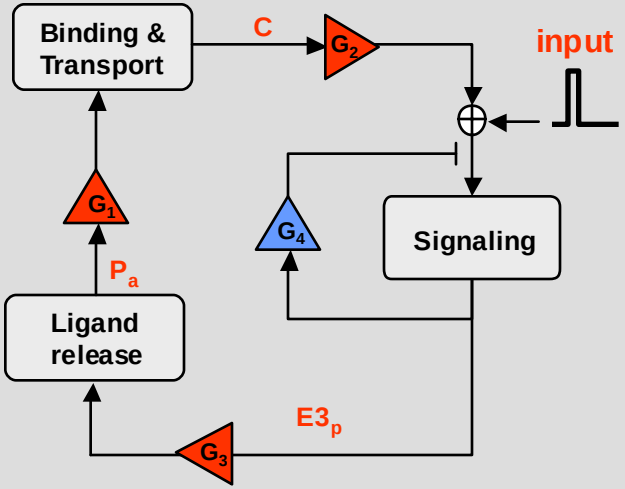


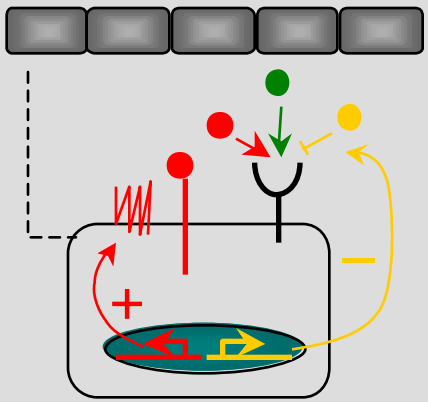
Autocrine Loops are Externalized Control Systems



Our Tools: Modeling and Analysis







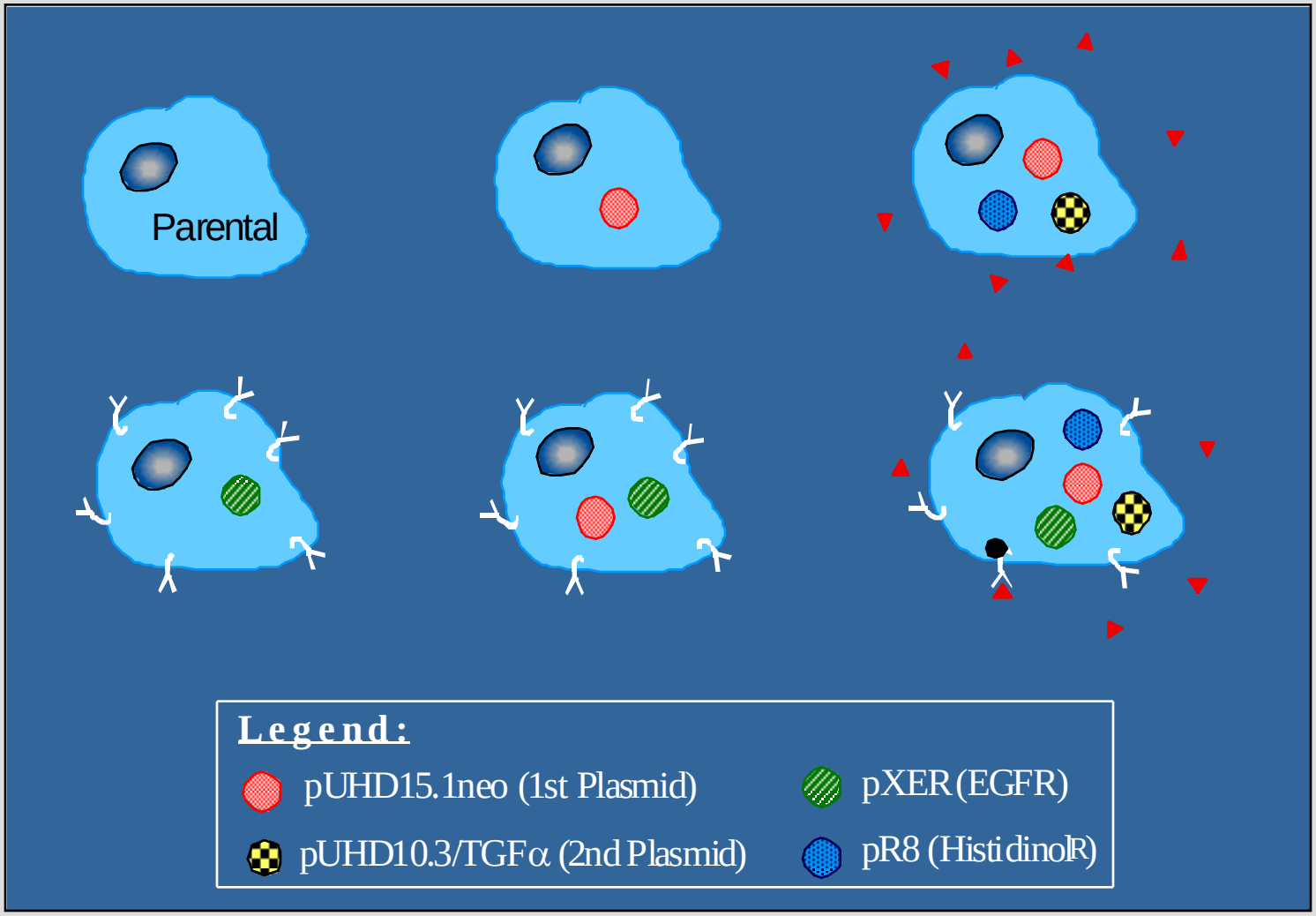
Models: deterministic and stochastic

lumped and distributed

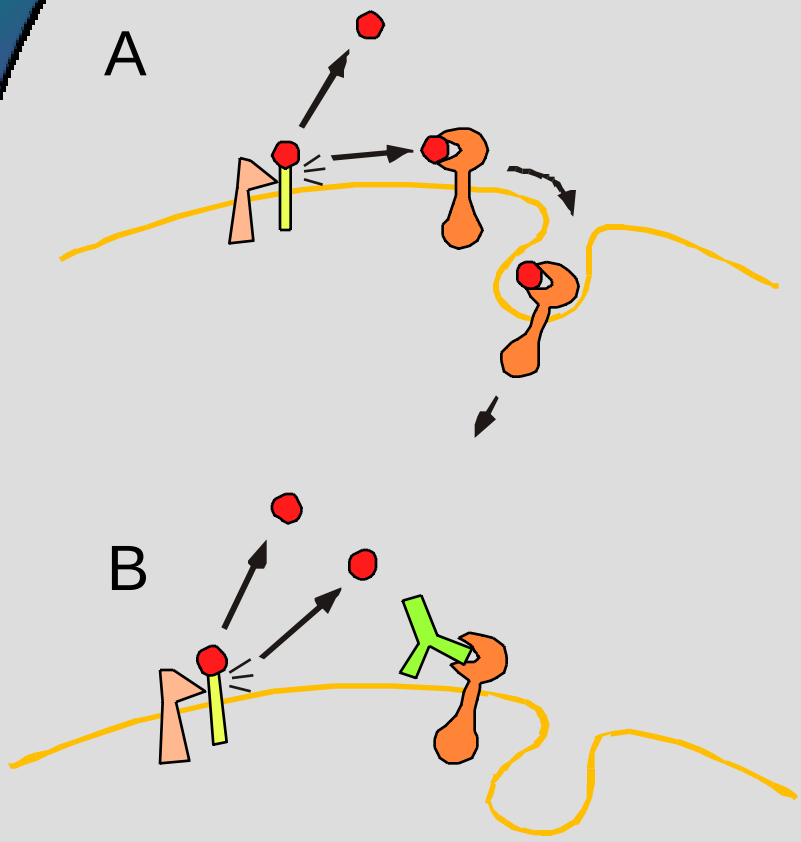
Analysis: theory and computation

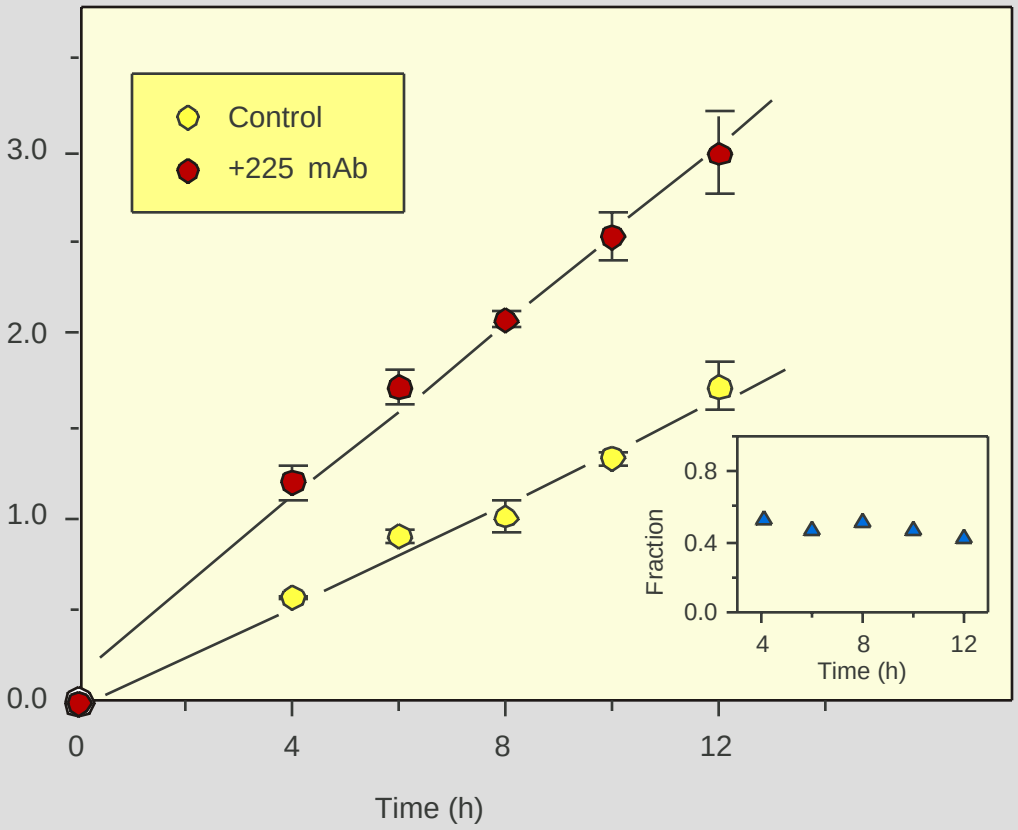
Applications: experimental systems

Reconstituting an Autocrine Cell

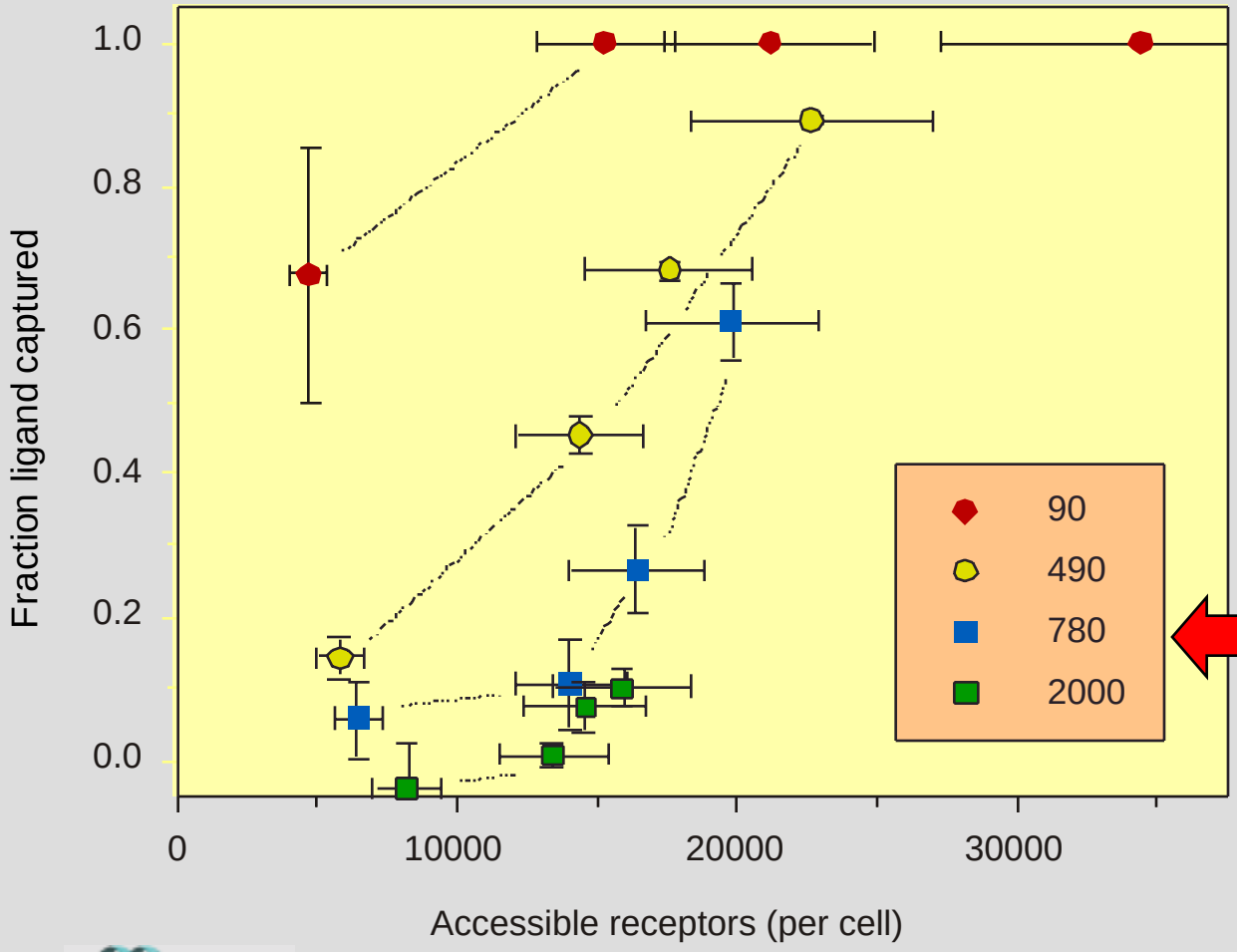


Fractional Capture of EGF



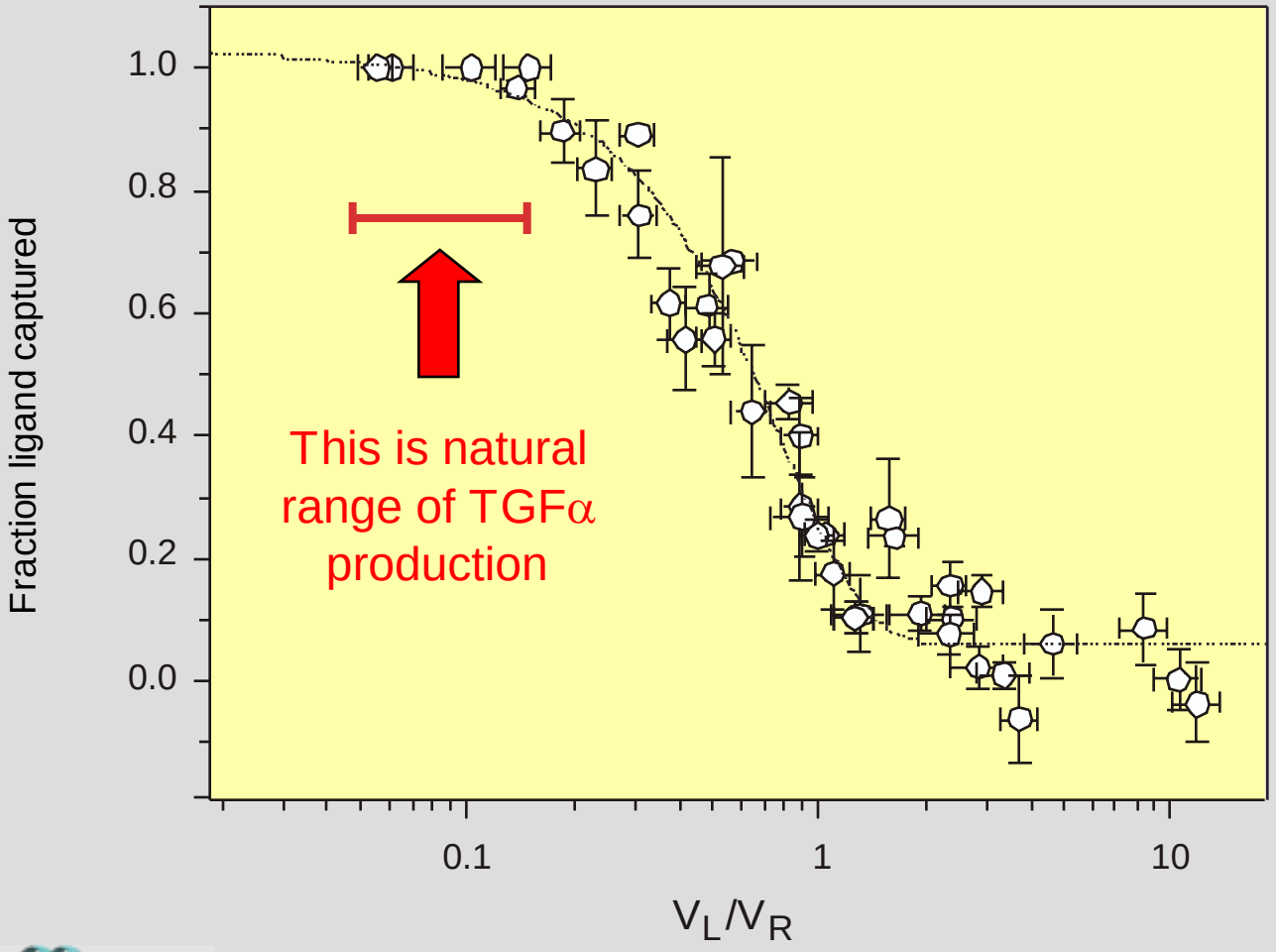


Autocrine Ligand Capture



Varying ligand expression

Simple Rule of Autocrine Capture

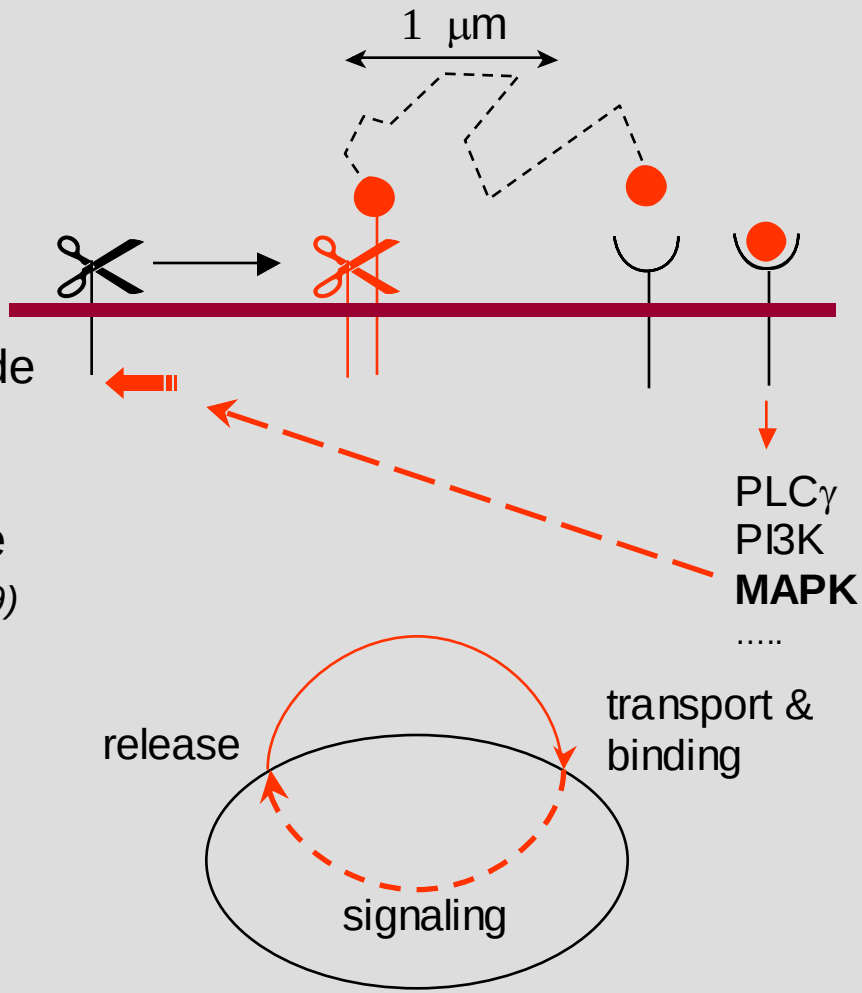


Ligand Comes Back to the Same Cell...
So What?

1) Autocrine ligands come back
(transport models)

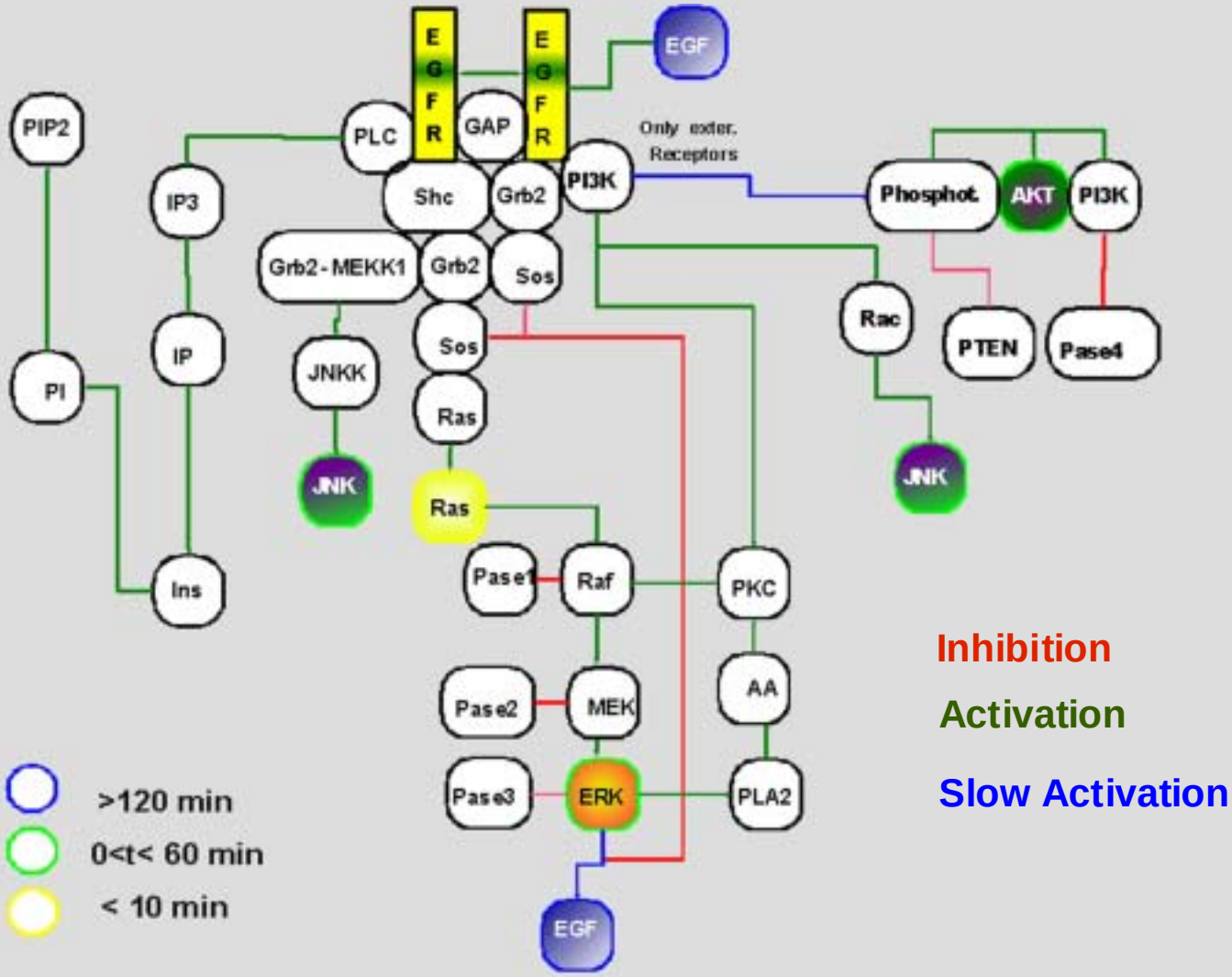
2) Bound receptor stimulates MAPK cascade
(common knowledge)

3) MAPK cascade stimulates ligand release
(Fan & Derynck, 1999; Gechtman et.al,1999)

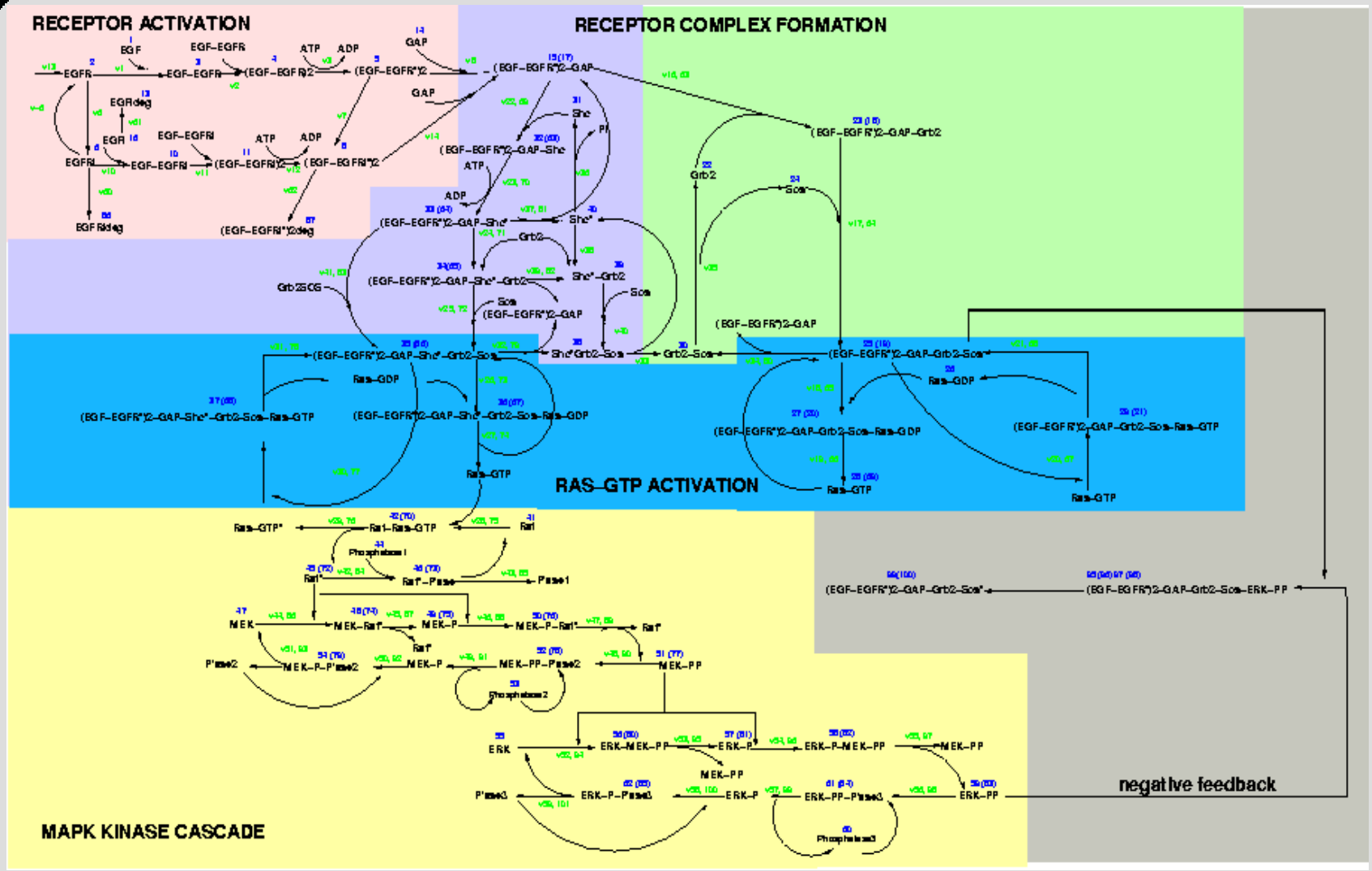


Ligand release is autocatalytic

EGFR Core Signaling Network

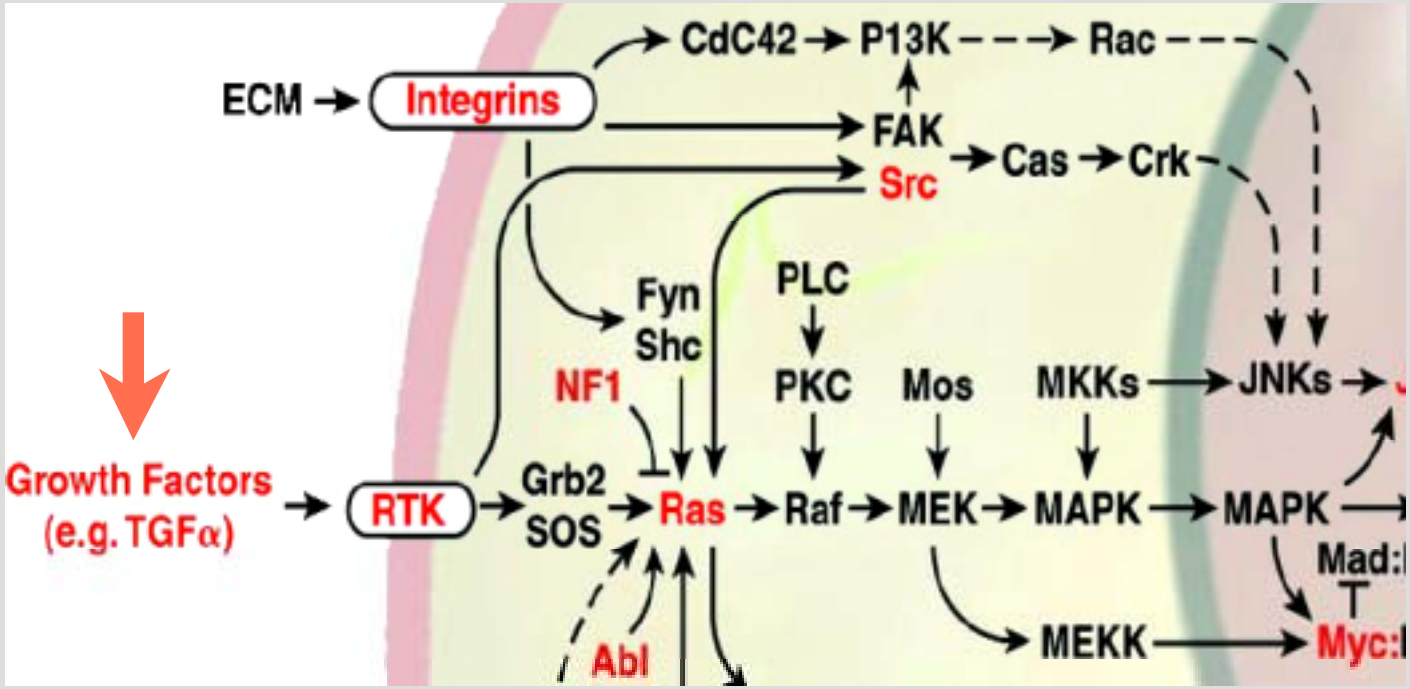


Biochemical Reaction Scheme



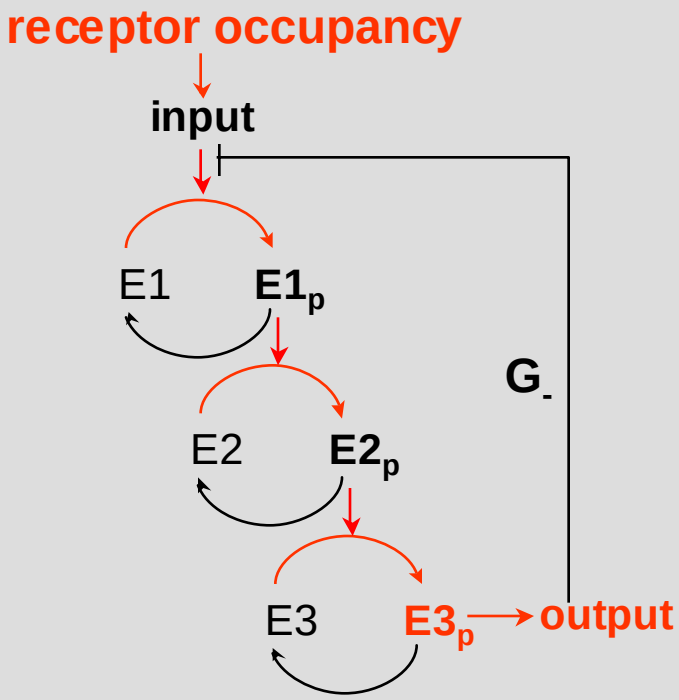
Schoeberl et al., *Nature Biotech.* [2002]

Signaling Through Growth Factor Receptors

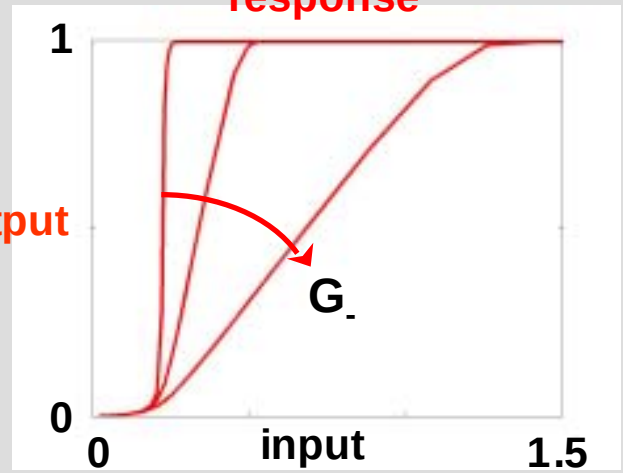


Ligand (Extracellular molecule)	→	Membrane **receptor**	→	Intracellular signaling cascade	→	Physiological response
INPUT	→	SENSOR	→	ACTUATOR	→	OUTPUT

High-level Model of MAPK Cascade

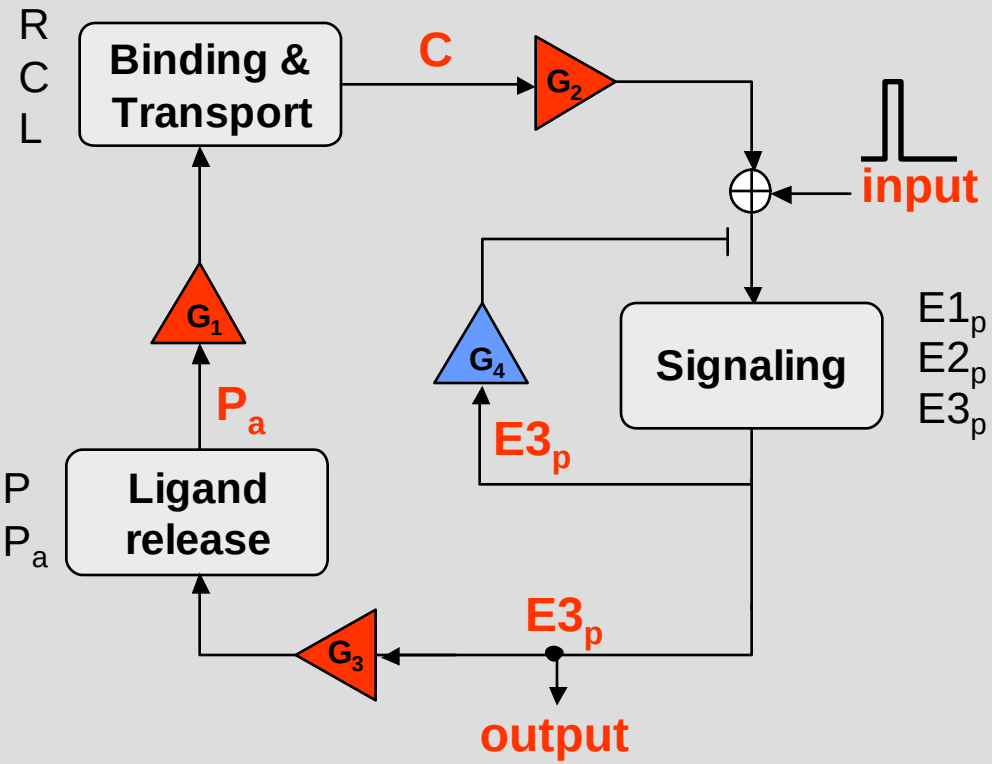


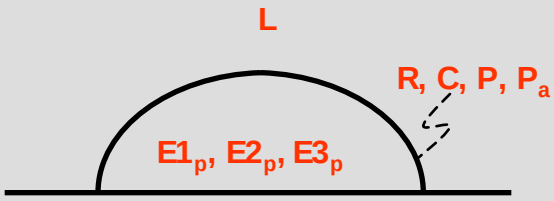
$$\frac{E_{3p}}{E_{3p} + E_3}$$ Output



- three stages
- each stage operates near saturation
- Michaelis-Menten kinetics

Model Autocrine Cell:





$$\frac{1}{k_{off}}\frac{d\bar{R}}{dt} = -\bar{R}\frac{G_1\bar{P}_a + Da\bar{C}}{1+Da\bar{R}} + \gamma(1-\bar{R}) + \bar{C}$$

$$\frac{1}{k_{off}}\frac{d\bar{C}}{dt} = \bar{R}\frac{G_1\bar{P}_a + Da\bar{C}}{1+Da\bar{R}} - \frac{\bar{C}}{1-\delta}$$

$$\frac{de_{1p}}{dt} = \frac{I_0 + G_2R_T\bar{C}}{1+G_4e_{3p}}\frac{1-e_{1p}}{K_{m,1}+(1-e_{1p})} - \frac{V_{\max,3}e_{1p}}{K_{m,3}+e_{1p}}$$

$$\frac{de_{2p}}{dt} = \frac{k_2e_{1p}(1-e_{2p})}{K_{m,2}+(1-e_{2p})} - \frac{V_{\max,4}e_{2p}}{K_{m,4}+e_{2p}}$$

$$\frac{de_{3p}}{dt} = \frac{k_3e_{2p}(1-e_{3p})}{K_{m,3}+(1-e_{3p})} - \frac{V_{\max,6}e_{3p}}{K_{m,6}+e_{3p}}$$

$$\frac{1}{k_e^P}\frac{d\bar{P}}{dt} = \mu(1-\bar{P}) - (\nu_0 + G_3e_{3p})\bar{P}$$

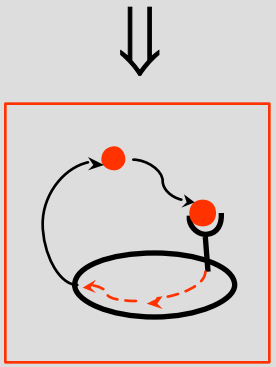
$$\frac{1}{k_e^P}\frac{d\bar{P}_a}{dt} = (\nu_0 + G_3e_{3p})\bar{P} - \bar{P}_a$$

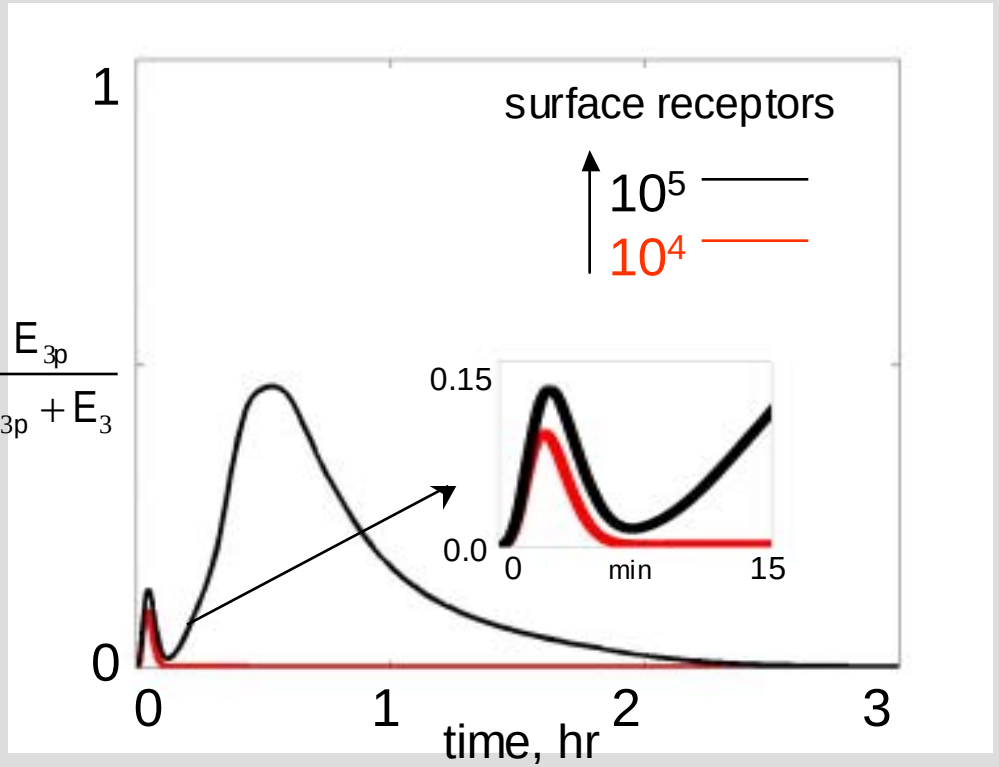
Autocrine Loops Modulate Extracellular Signals

Multiple Excitations in a Closed-Loop System

Primary excitation: *minutes*

Secondary excitation: *hours*



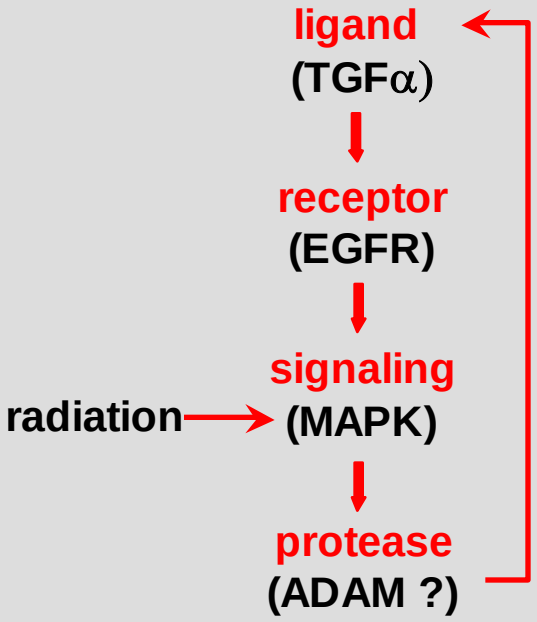


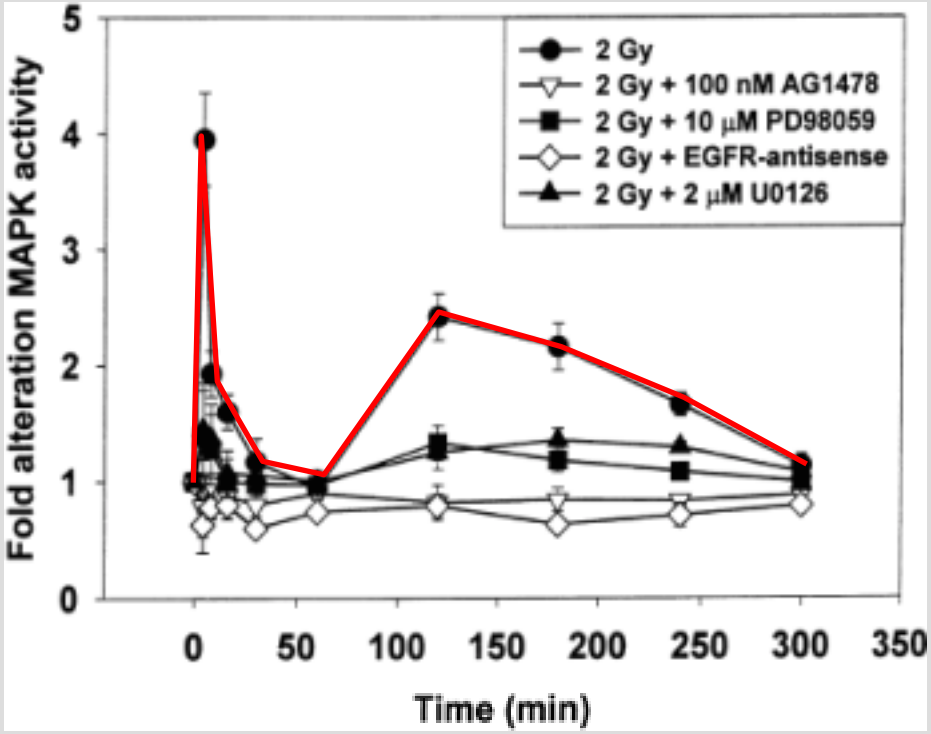
Does this really happen?

Multiple Excitations (Experiment)

Dent et.al., *Radiation Research*, 2000

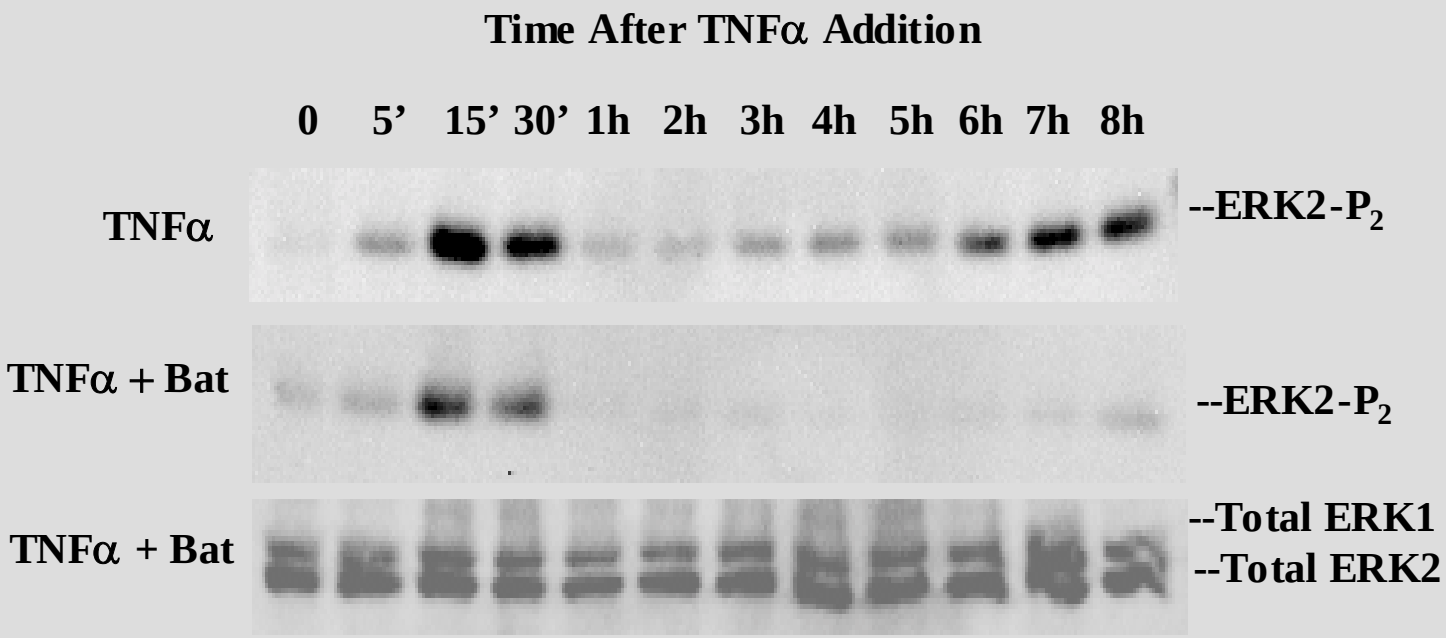
"Radiation-induced release of TGFα activates the EGFR and MAPK pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death"



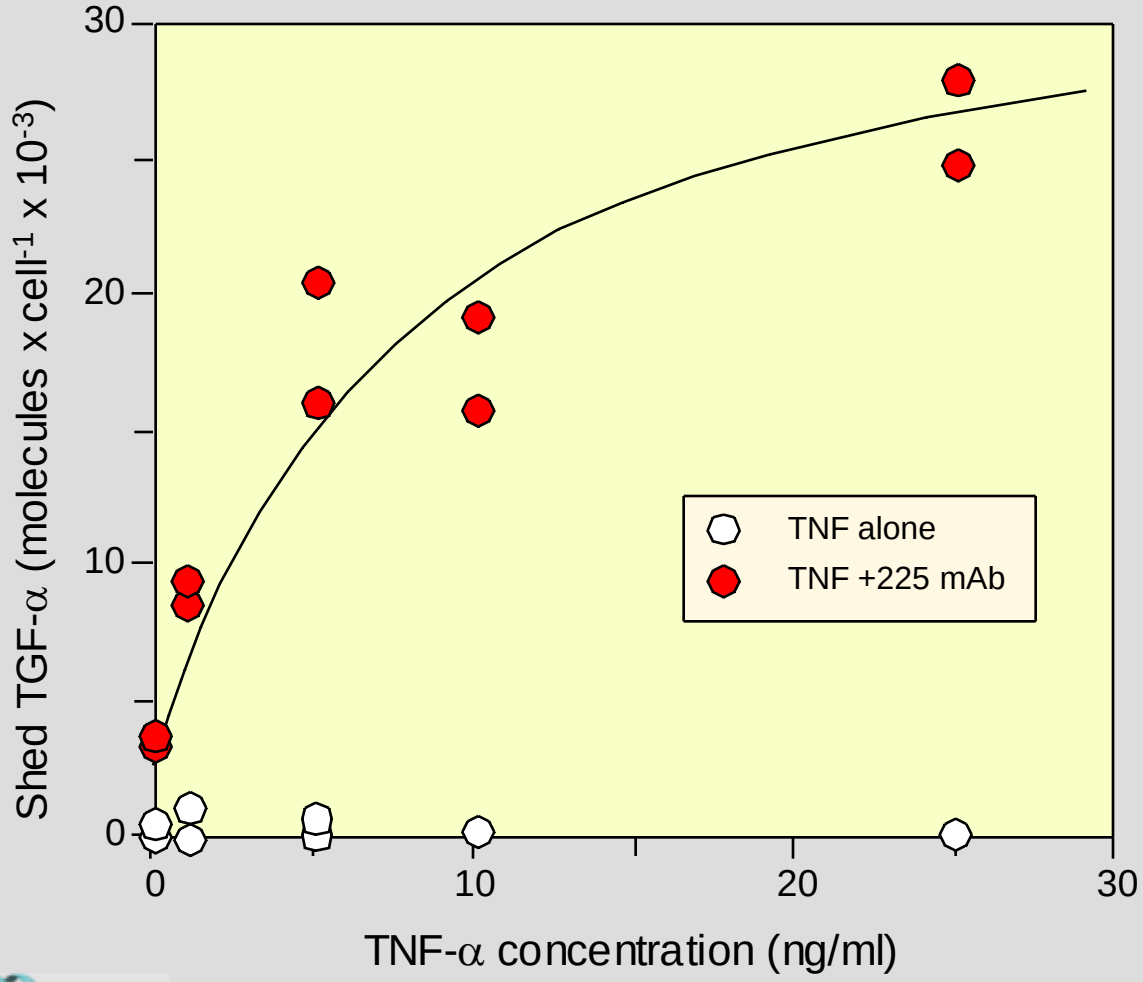


The model accounts for the secondary MAPK excitations in response to pulses of radiation

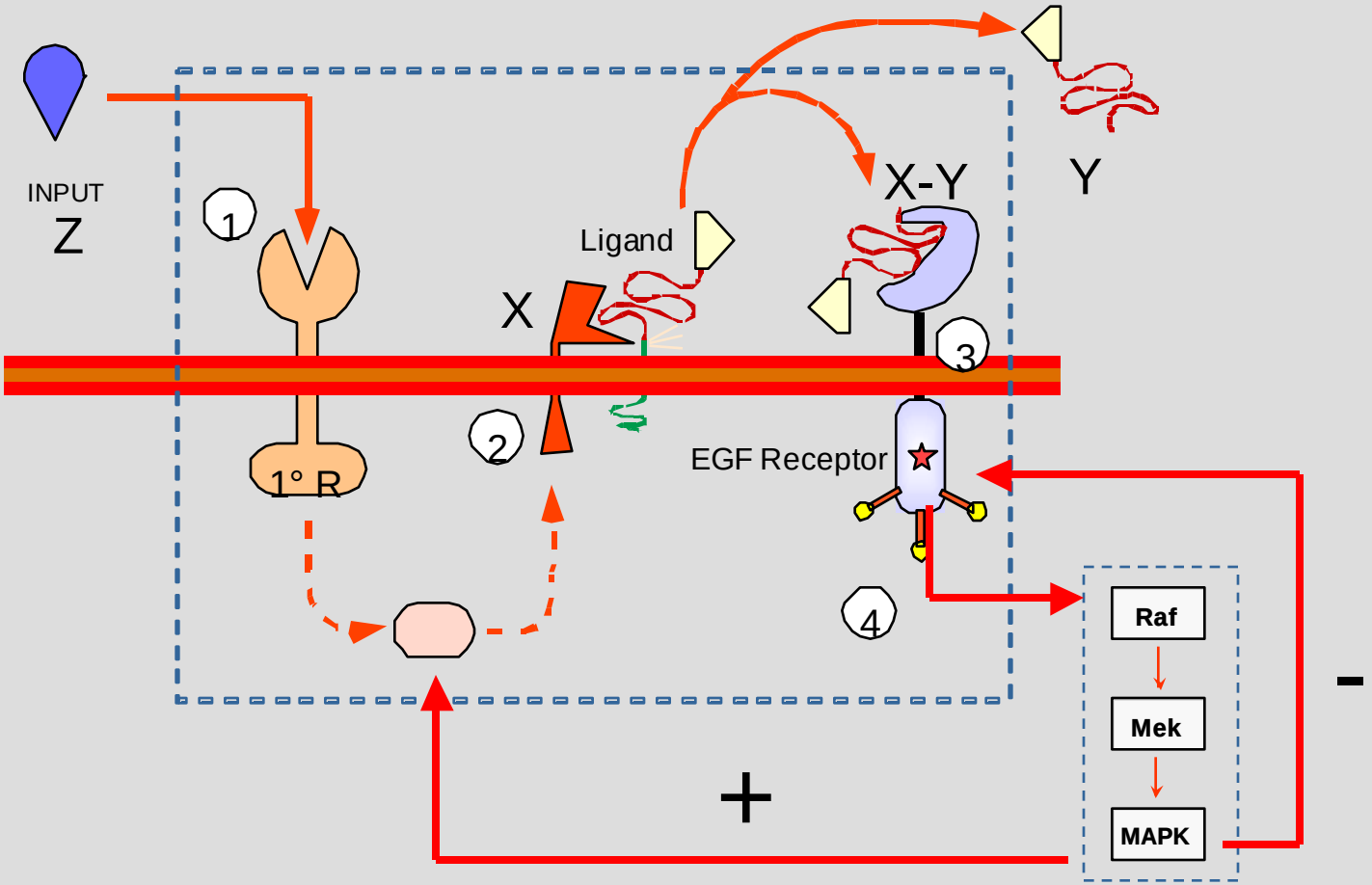
TNFα Stimulates Two Waves of MAPK Activation



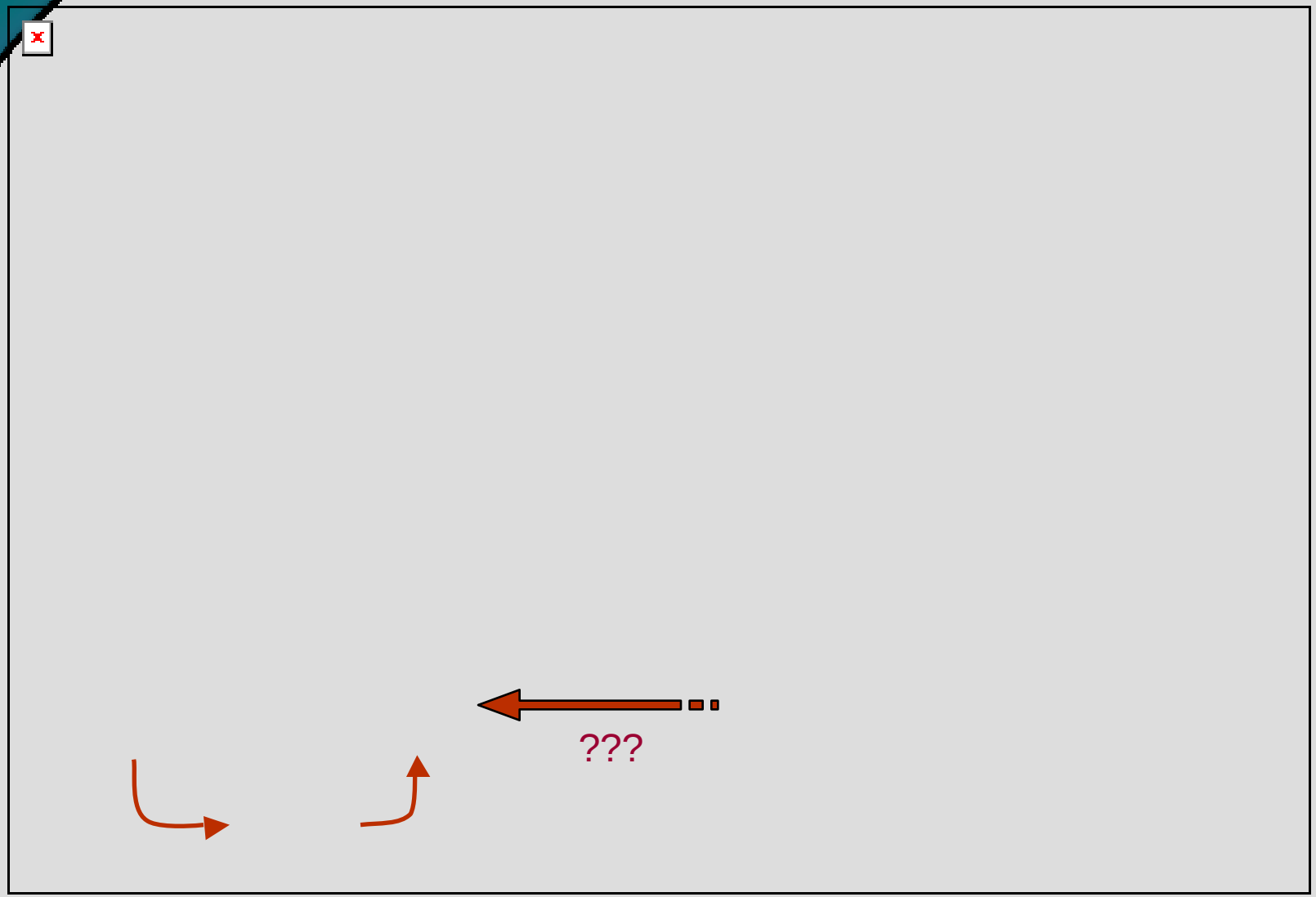
Shedding Response is Graded



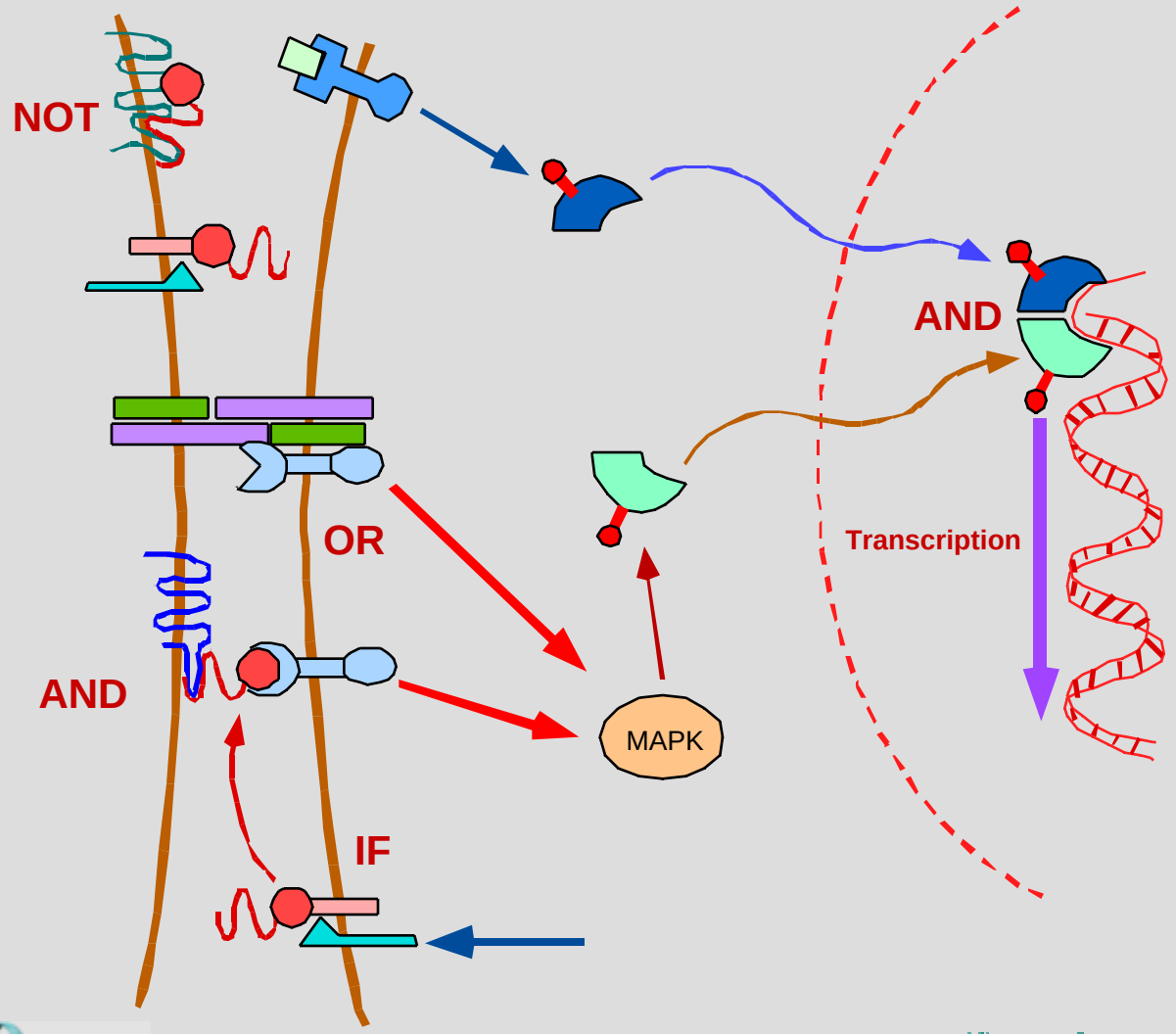
Autocrine Signaling as a Control Circuit

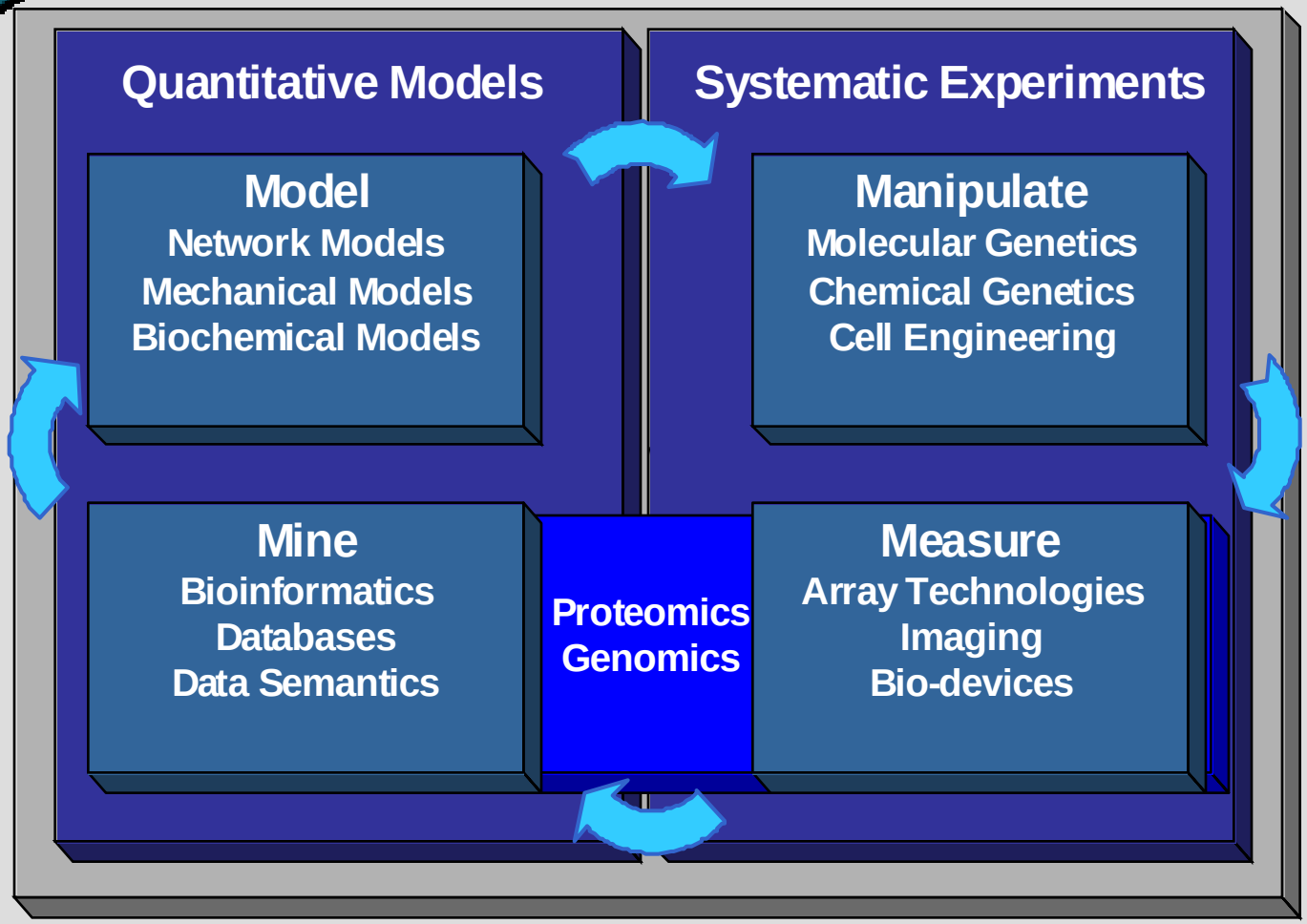


Interrogative Signaling



Information Processing at the Cell Surface





Computation:

- **elucidate hypotheses *(mining)***
- **facilitate predictions *(modeling)***

Systematic experimentation:

- **quantitative**
- **multi-variable**

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